A HANDBOOK FOR ADOPTION DISCLOSURE

A Guide to Genetic, Developmental and Medical Considerations

A HANDBOOK FOR ADOPTION DISCLOSURE:

A Guide to Genetic, Developmental and Medical Considerations

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INTRODUCTION

The following is a guideline to assist you in evaluating the request for a search, namely on behalf of:

- the person requesting the search or
- the person on whose behalf a search is requested.

This is to be conducted for a subject with severe illness (physical and/or psychological) who will derive a direct medical benefit, related to either the treatment or diagnosis or if

- the person for whom it is sought

If they are or may be subject to a **severe illness** (physical and/or psychological) and that they will derive a direct medical benefit (related to treatment or prevention) from the result of the search.

Who May Request a Search

Those who may request a search are:

1. The adopted person.
2. The son or daughter of the adopted person.
3. Any other descendant of the adopted person.
4. The adopted person's birth parent.
5. The adopted person's birth grandparent.
6. The adopted person's birth sibling.
7. Any other birth family member of the adopted person.
8. In a case where it was the adopted person or birth parent who suffered from the severe mental or physical illness and the adopted person has died, any of the following persons may request a search:

    i. The adopted person's or birth parent's spouse.
    ii. The executor of the adopted person's or birth parent's spouse.
    iii. A person who is,

        A. a member of the College of Physicians and Surgeons of Ontario, a member of the College of Psychologists of Ontario or a member of the College of Nurses of Ontario who holds a certificate of registration in the extended class,

        or

B. legally authorized to practise medicine or psychology in a jurisdiction outside of Ontario.

What a search will reveal is the birth parents, grandparents or siblings of the adopted person or, if the search comes from one of these people, the adopted person and their sons, daughters or any other descendants. Searches may also be conducted to find an adoptive parent, in cases where the adopted person is a minor.

Note: This handbook was prepared to assist you in your understanding of some common disorders for which a search may be requested. It is not meant to fetter your judgement, or as a substitute for your experience and expertise when assessing a request for disclosure. Each case should be looked at on a case-by-case basis and assessed according to the legislation. This handbook, therefore, is merely one 'tool' you may choose to consult in the process of assessing a request for disclosure.

Table 1 - General Guide to Who May Qualify

The following are general principles that will assist you in your decision in most cases.

A	Severe Illness	A search will only be conducted for *a severe illness*. *Severe illness* should be understood to mean any of the following: 1. Life threatening illness, Ex. Familial Adenomatous polyps or 2. A chronic, protracted illness whose course will inevitably decline, Ex. Multiple Sclerosis, Huntington's chorea, etc.
B	Severe illness that is genetically transmissible	Any *severe illness*, whose disease has a genetic pattern of transmission. *A severe illness* whose presence is associated with and an increased risk of progression of the disease such that it would lead to the incapacity to function in an independent manner. Or situations in which there is a possible intervention which would prevent, or allow for benefits from early diagnosis and/or treatment, Ex. Familial ovarian cancer. or Knowledge of *the condition* would allow free choice concerning reproduction and may *lead* to a choice not to reproduce, Ex. Huntington's Chorea.
C	Severe disease with genetic transmission pattern but no effective intervention	Those cases where there is a known genetic disorder for which there is no effective intervention but the knowledge of the increased risk for the disease would have serious social or functional implications, Ex. ALS., Alzheimer's.

Further Discussion of A, B, and C

Sections A, B and C are further developed in the body of the Handbook. Please refer to the Handbook for more information.

Note: Throughout this document, the word *client* refers to the person seeking the search, and the person being sought is referred to as the relative, although this may not be the actual case genetically.

GENETICS AND ITS IMPLICATION FOR ADOPTION

This section, although somewhat technical, is useful for the following reasons:

(1) Have a general understanding of inheritance.
(2) Patterns of inheritance if identified, can tell you who will be affected, potentially affected or not affected at all, and therefore guide you in your decision.
(3) The concepts and vocabulary here should allow you to:
    (i) Understand the general, if not, the specific implication of genetic testing reports.
    (ii) Allow you to ask the correct question about genetic testing, inheritance, etc.
    (iii) Allow you to communicate more effectively with health professionals.

The key questions that determine whether a request ought to be granted or not, based on genetics are:

1. Are there known genetic patterns for the disease that are expressed among family members who are linked by a common heritage?

2. Are there higher incidences of the genetic patterned disease in **identifiable** and **definable** population(s) or group(s)?

3. Are there reliable and valid diagnostic tests available for a specific (genetic) disorder?

4. Are there interventions available if susceptible subjects are identified as positive?

5. Is there variable penetrance for this disease or pleiotropism as in Tuberous Sclerosis?

6. What is/are the ethical considerations in notifying an individual of their potential or inevitable diagnosis of the disease in question? Harm vs benefit.

7. Is it ethical to give the information to a *'client'* or *'relative'* via phone or letter? What are the risks in doing so?

If questions 1 and 2 are answered in the positive (yes), then the answers to 3 and 4 should also be positive before releasing the information. In cases where there is no specific test available but the exact pattern of inheritance is known for the disease Ex. Autosomal dominant, sex linked, etc., and then these may also be considered.

However, there will be times when question 4 may be 'no' and yet the information should likely be conveyed to the party concerned. *Then this should be guided by questions 5, 6 and 7.*

In order for questions 5, 6 and 7 to negate question number 4, there must be objective evidence of benefit, or direct evidence of harm reduction, attested to by a physician licensed to practice in Canada. **The statement that it *could be helpful to treatment or diagnosis* is not sufficient it must be essential, understood to mean the absence of this information would result in misdiagnosis, or incorrect treatment or serious harm to the *'client'* or *'relative'*.** Although health professionals will frequently make the statement that a certain piece of information would be helpful, there must be convincing evidence that this information is not just *helpful* but **necessary,** according to the criteria set out above.

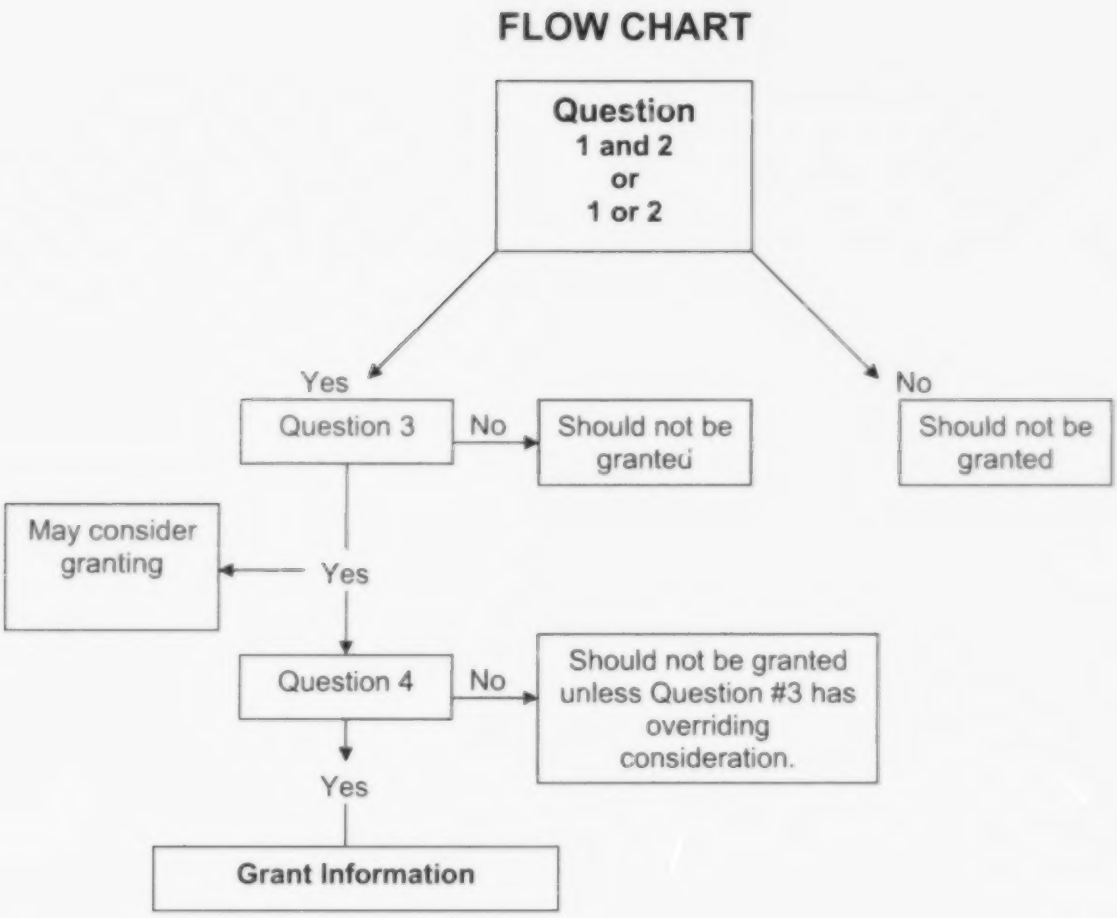


Fig. 1

The flow chart will apply in most cases – however, there will be those cases for which no intervention is possible, but the outcome is certain and the consequences are grave. Give careful consideration to the issues raised in 5, 6 and 7. See explanatory note on questions 5, 6 and 7 on the previous page. An example would be Huntington's Disease (next page).

Huntington's Disease as an example

Huntington's disease is characterized by abnormal voluntary movements, gait disturbances (balance), abnormal eye movements, dysarthria (difficulty speaking) rigidity, cognitive and mood disturbances and inevitably dementia. This autosomal dominant pattern has severe consequences (dementia) but there is NO known treatment.

Here, the answer to questions 1, 2 and 3 are 'yes' but question 4 (intervention) is negative. There could be either associated *harm* (anxiety, depression, etc.) as a consequence or *benefit* able to prevent conception, thereby, not passing on this lethal disease, etc. One would have to carefully consider such facts before deciding the course of action. It is also important to consider how to best relay the information to the client or relative. If the client has specifically consented or requested that the custodian give this information via the *client's* attending physician, it may be preferable to proceed in this manner. This may not always be possible.

PART I

GENETICS AND ITS IMPLICATION FOR DISCLOSURE

Today, many more infants and children with severe genetic abnormalities are surviving into the reproductive age and beyond. For reasons that are not entirely clear, we are also seeing more mutations than before.

Genetics is a complex subject that can be overwhelming especially for those without a strong background in the biological sciences. This section on genetics is the most technical and difficult section in the Handbook. Do not be discouraged or "turned off" by this fact. This first section tries to help you understand who is and who might potentially be affected. Try not to get bogged down in detail. Rather, try first to recognize the names of the main types of disorders ex. autosomal, sex linked, etc. Then, come to understand the modifying factors, like dominant, or recessive. Your aim is to understand not only who might be affected but also how severely.

Thus, you might ask the following:

(1) What type of genetic disorder is this, ex. autosomal dominant?
(2) If it is for instance, autosomal dominant, who should be affected?
(3) Are there any modifying factors such as, homozygous, heterozygous penetrance, etc.?

If you can answer these questions, you should have a good idea of who is affected and to what degree. Of course, you must know what the main effect of the condition is ex. Down's syndrome often exhibit below average intelligence and decreased longevity.

BASIC SCIENCE OF GENETICS

While the intention of this Handbook is not to make you into scientists or geneticists – some minimal background is essential if you are to grasp what is important for your decision making.

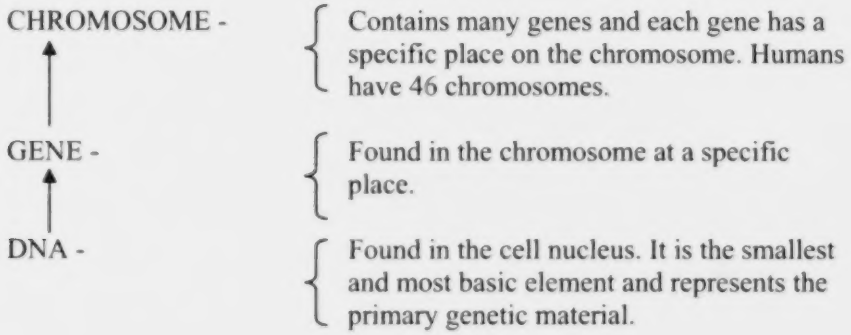
Taking the time to become familiar with the terminology and concepts presented here will allow you to better understand what you are dealing with and to be able to use the flow chart more effectively. A glossary of genetic terms and related concepts is provided in the Appendix of this Handbook. Some terms are explained within the body of the text itself.

MENDELIAN INHERITANCE

The term MENDELIAN INHERITANCE is commonly used to refer to the different patterns of inheritance demonstrated or expressed by a **single gene** characteristic (ex. tallness) and to disorders found to be the result of **defects in a single gene**. This type of pattern is said to be **Mendelian**, named after the Augustinian Monk, Gregor Mendel, who is now considered the father of Genetics. As a result of Mendel's work, you will often encounter the term 'gene' which means:

> A segment of a DNA[1] molecule that contains all the informations needed to pass on a specific characteristic from parent to the progeny (also called the first filial generation or F_1). It is very simply the basic unit of heredity that is self-reproducing.

It is important to note that genes occupy specific locations on the chromosome (a chromosome is that part of a cell that transmits a linear thread of DNA, which in turn transmits the actual genetic information.) A single chromosome may, therefore, carry many genes.

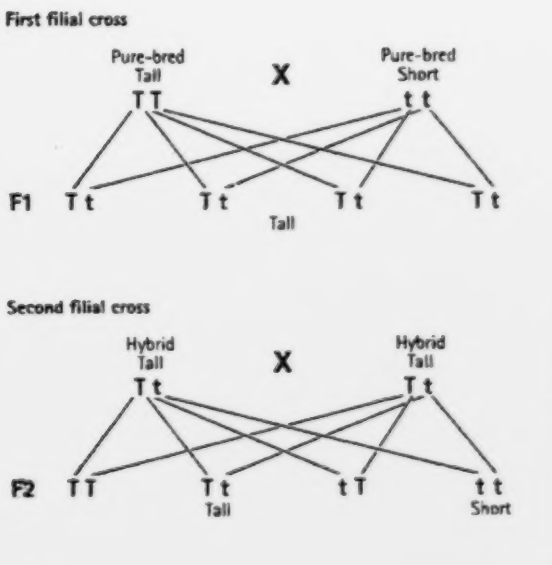


Now, if we are to understand all the terms and ideas needed to make decisions about genetic abnormalities, we will need a bit more science.

[1] DNA – stands for deoxyribonucleic acid (a sugar) that constitutes the primary genetic material of all cellular organisms.

Let's return to Gregor Mendel's experiment. To start, he bred plants that varied by one characteristic ex. tallness, shortness, colour, etc.). Thus, if plants were bred for a feature like **tallness,** with plants that exhibited **shortness**, all the offspring of this breeding resulted in progeny (offspring) which he termed as the first filial generation or F_1 - they were **all tall**. If plants from the F_1 generation were interbred (bred with each other), then this led to a second filial generation, termed F_2. Some of these second generation plants were *tall* while others were *short*. Interestingly, this always resulted in a ratio of 3:1 (3 tall to 1 short). Mendel concluded that the resultant outcome, tallness/shortness was a result of a pair of factors, one from each parent.

The pure bred plants, with two identical genes used in the initial cross-breeding are referred to as **homozygous** (think of them like purebreds). The mixed or hybrid F_1 generation which contained one gene for tall and one gene for short, are referred to as **heterozygous** (think of them as muts). The genes responsible for these *contrasting characteristics* were termed **allelomorphs** or simply **alleles**.



Note: 3 tall and one short phenotype were produced in the F_2 generation. The short phenotype is pure for short (homozygous tt); whereas amongst the tall phenotypes, one is pure for tall (homozygous TT) while the other two are not (heterozygous Tt or tT).

Fig. 2
An illustration of one of Mendel's breeding experiments and showing the genotype.[2]

From the work of Mendel, three general laws have been developed. There are some exceptions to these rules but they will be pointed out as we come across them[3]:

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[2] One term you will frequently encounter, refers to:
(1) the entire genetic constitution of an individual
or (2) the alleles present at a particular location on the chromosome(s)
(3) type of species (of a particular class or genes)
This term is genotype.

[3] TURNPENNY, P. and Ellard, S: Emery's Elements of Medical Genetics, 12 ed. (Oxford: ELSEVIER CHURCHILL, Livingstone Publ., 2005) p. 105.

THE LAW OF UNIFORMITY

The *law of uniformity* refers to the fact that when two homozygotes with different alleles are crossed, all the offspring in the F_1 generation are identical and heterozygous. In other words, the characteristics do not blend, and can reappear in later generations.

THE LAW OF SEGREGATION

The *law of segregation* refers to the observation that each individual possesses two genes for a particular characteristic, only one of which can be transmitted at any one time. Rare exceptions to this rule can occur when two allelic genes fail to separate because of chromosome non-disjunction at the first meiotic division.

THE LAW OF INDEPENDENT ASSORTMENT

The *law of independent assortment* refers to the fact that members of different gene pairs segregate to offspring independently of one another. In reality, this is not always true, as genes that are close together on the same chromosome tend to be inherited together, i.e., they are said to be linked.

We will be primarily concerned with disorders that result from:

1. Loss or gain of a whole chromosome.
2. Abnormalities of single genes.

We will see how the properties implied by these laws interact with chromosome behavior to cause hereditary disorders. From time to time, I will introduce a bit more science. Nevertheless, this very simplified presentation should suffice to allow you to assess the significance of individual disorders.

At the end of this section, the Punnett's square will indicate all the possible outcomes of *heterozygous inheritance*.

Patterns of Inheritance

Genetics is usually written as pedigree diagrams using specific symbols for female, male, affected male, affected female, carrier, etc. The chart below is provided for you so that you can follow such a pedigree. This will allow you to:

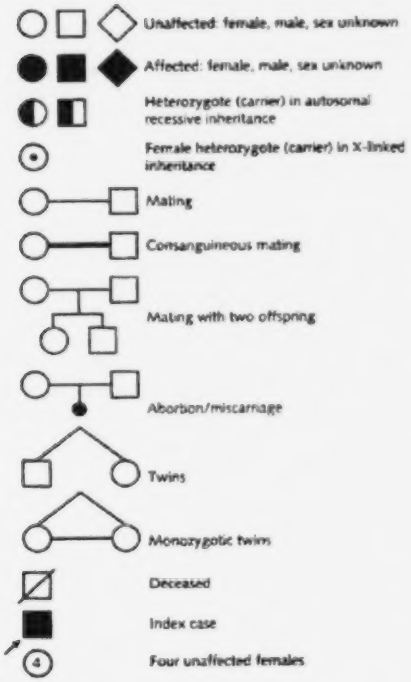
(1) read reports provided to you and understand what the pedigree diagram is telling you.

(2) allow you to consult standard texts and article to answer specific genetic outcome questions, ex. understanding the outcome of a mating involving one affected parent with an autosomal dominant disorder.

(3) know what question to ask when seeking a consult.

(4) improve your communication with health professionals.

Fig. 3 Standard Pedigree Symbols:[4]



It is known that over 11,000 traits or disorders in humans demonstrate a single gene **(unifactorial) or Mendelian inheritance**. However, many common characteristics such as height and many common familial disorders such as diabetes, hypertension, etc. do not follow a Mendelian pattern.[5]

THE AUTOSOMAL DISORDERS

A trait or disorder is said to demonstrate autosomal **inheritance** when it is caused by a gene situated on an **autosome[6].** In contrast, if the gene appears on one of the SEX chromosomes, the trait or disorder is said to exhibit sex**-linked inheritance.**

You will frequently encounter a statement that this or that disease is **autosomal dominant**. In terms of risk, this means that an individual with a dominant trait or disorder has a chance of passing on either a normal allele or an abnormal one. Therefore, any progeny will have a risk of 1 in 2 (50%) chance of inheriting the disorder or trait. If an autosomal dominant disorder can appear in several different ways, then it is said to be **pleiotropic**, i.e., a single gene that can give rise to two or more apparently unrelated effects. An example of this is seen in Tuberous Sclerosis where an affected individual can present with either *learning difficulties, epilepsy or a facial rash (adenoma sebaceum).*

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[4] Adapted from: Pang D. and Newson, T. *A Crash Course in Pediatrics.* (Toronto, Mosby, 2005) p. 194.
[5] Ibid.
[6] Autosome: any ordinary, paired chromosomes. In humans, there are 22 sets of paired (autosomal) chromosomes and two sex chromosomes, for a total of 46 chromosomes.

It is also important to note that autosomal dominant disorders, can show striking variations from person to person, even within the same familial group. Thus, in autosomal dominant polycystic kidney disease, an individual may have anything from renal cysts to complete renal failure. This variability of expression is termed **variable expressivity.** It is also possible for some individuals to have no obvious expression of the disease – it appears to skip a generation. This is termed **non-penetrance**, while those exhibiting a mild form of the disease are said to have **reduced penetrance**. (Please refer back to item number 5 on page 4).

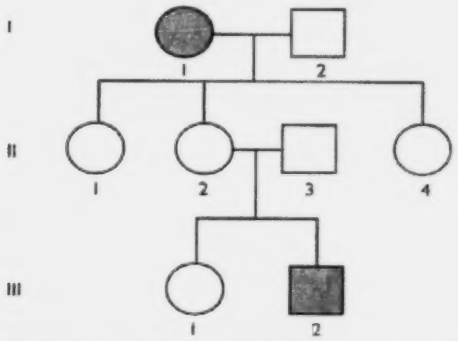


Fig. 4 - Example of non-penetrance. I1 and III2 have otosclerosis. II2 has normal hearing but must have the gene. The gene is non-penetrant in II2[7]

While most disorders result from an affected parent, it is possible to have an autosomal dominant disorder appear with no family history. This arises usually from an error occurring in the transmission of a gene and is termed a **new mutation**. One has to rule out the possibility of **non-paternity** in such cases to be sure it is a new mutation.

It is also possible for two traits to be paired at the same time and they will be expressed in the heterozygoses state. An example is the blood type AB, thus A and B groups exhibit **co-dominance.**

Homozygosity for Autosomal Dominant Traits

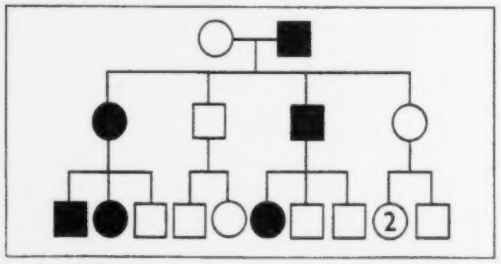
Thus far, we have been talking mostly about the heterozygous state. However, although most abnormalities arise in the heterozygous state, there are a few known to arise from couples who were both homozygous for a dominant trait. Consequently, the progeny of these couples could be homozygous for that trait or disorder. When this happens, such individuals tend to be more *severely affected* and/or at an *earlier* onset, (ex. **Familial Hypercholesterolemia**).

[7] Lissauer, Tom, Clayton, Graham, Illustrated Textbook of Pediatrics, 2nd Ed. Mosby International Limited, 2001. p.89

Fig. 5 - Autosomal Dominant Inheritance[8]

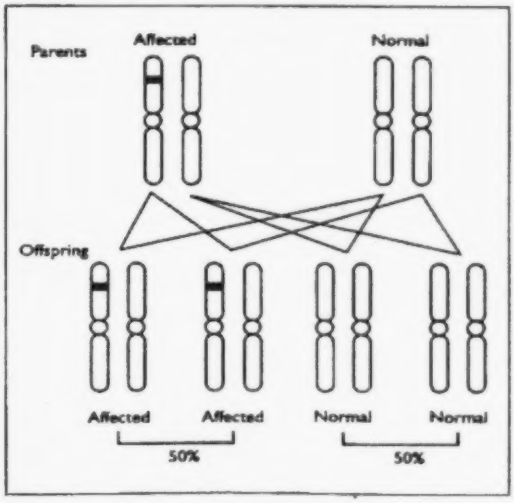
Examples of autosomal dominant disorders

Achondroplasia	Neurofibromatosis
Ehlers-Danlos syndrome	Noonan's syndrome
Familial hyper-Cholesterolemia	Osteogenesis imperfecta
Huntington's disease	Otosclerosis
Marfan's syndrome	Polyposis coli
Myotonic dystrophy	Tuberous sclerosis



Typical pedigree of an autosomal dominant disorder.

Autosomal Dominant Inheritance



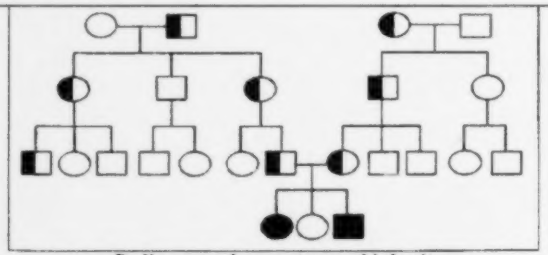
Autosomal Recessive Inheritance

Disorders and traits arising from recessive inheritance are only manifested by individuals who have two copies of the recessive allele. They are thus *homozygous*. Persons who are *heterozygous* for the trait or disorder do not show the trait or disorder. Instead they are **carriers** (capable of passing it on to the next generation).

Fig. 6 - Autosomal Recessive Inheritance[9]

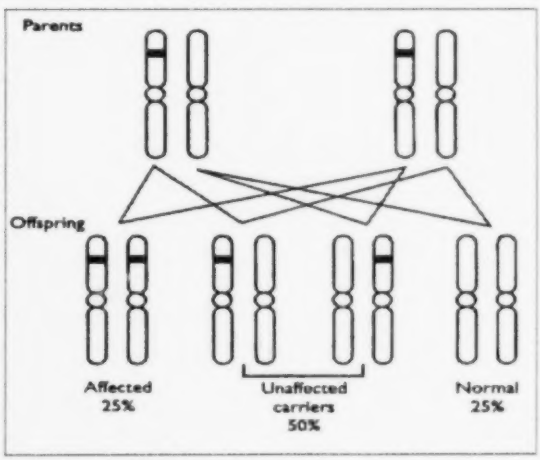
Example of autosomal recessive disorders

Congenital adrenal hyperplasia	Oculocutaneous albinism
Cystic fibrosis	Phenylketonuria
Friedreich's ataxia	Sickle cell Disease
Galactosemia	Tay-Sachs disease
Glycogen storage disease	Thalassemia
Hurler's syndrome	Werdnig-Hoffmann disease



Pedigree to show autosomal inheritance

Autosomal Recessive Inheritance



[8] Ibid. p. 88
[9] Ibid. p. 89

The actual risk can be calculated and expressed as follows:

Let A = a normal dominant allele
Let a = a recessive abnormal or mutant allele

Then any offspring born to **two heterozygous parents** would have one of the following genotypes:

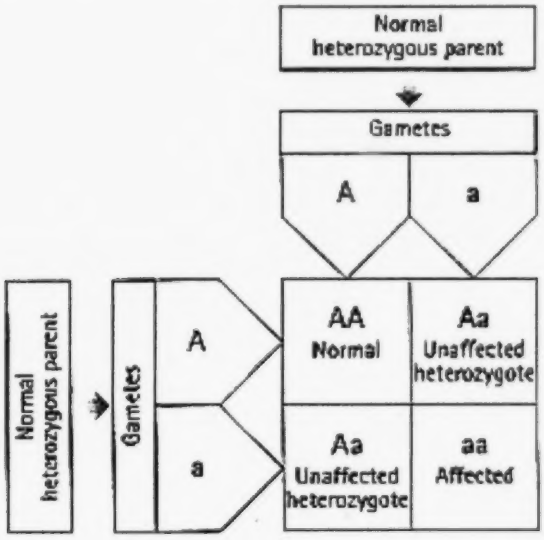


Fig. 7 - Punnett's square showing possible gametic combinations for heterozygous carrier parents of an autosomal recessive allele.[10]

- 25% chance (1 in 4) of being **homozygous affected.**
- 50% chance (1 in 2) of being **heterozygous unaffected**.
- 25% chance (1 in 4) of being **homozygous unaffected**.

Where genetic testing is available for a particular heterozygous disease, the parent's zygosity should be provided. This will allow you to calculate the odds that an individual be affected by the disease using the Punnett's square above. However, unless the individual in question is actually tested, the outcome cannot be determined.

[10] Turnpenny, P., et tal, Emery's Elements of Medical Genetics 12th Ed. Ibid., p. 109

CONSANGUINITY

The appearance of rare recessive traits may strongly suggest **consanguinity** (progeny produced by two biologically related parents). For example, if the rare metabolic disorder **Alkaptonuria** is looked at, it is noted that 25% of the parents are consanguineous. The reason that this disorder appears more frequently in consanguineous unions, is that there is a greater chance for similar alleles meeting up and reproducing this condition.

The *risk* of producing an Abnormal or Mutant Gene:

> If there is both a *normal dominant allele* and *recessive mutant allele*, then the various possible combination (of gametes) that two heterozygous parents could produce are:
>
> (1) 1 in 4 (25%) chance the progeny will be homozygous affected.
> (2) 1 in 2 (50%) chance of being heterozygous and unaffected.
> (3) 1 in 4 (25%) chance of being homozygous unaffected.
>
> Please note that if an individual who is homozygous for an autosomal recessive disorder marries a carrier of the same disorder, their progeny have a 1 in 2 or 50% chance of being affected (this is termed **pseudo-dominance**).

Since genes for some condition such as **Retinitis Pigmentosus** can present on any of six possible loci, it is possible that these recessive genes are at different loci. Thus even parents who are autosomal dominant may produce normal children. This is due to the fact that the loci for the two parents are at different loci and, therefore, do not unite. The individual will be unaffected. This is termed **locus heterogeneity** and will result in unaffected children.

SEX LINKED DISORDERS

The sex chromosomes are chromosome X (female) and chromosome Y (male). A trait or a disease is said to be sex-linked if it is on any one of these two chromosomes. Genes carried on the X chromosome are termed **X-linked** while those on the **Y chromosome** are termed Y-linked.

X-Linked Recessive Inheritance

An X-linked recessive trait is one determined by a gene present on the X chromosome and *usually only manifested in males*.

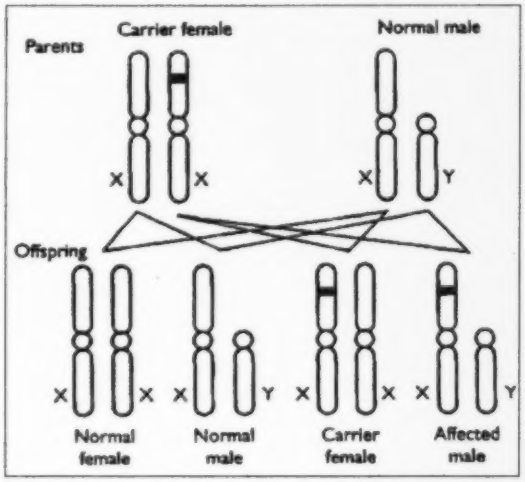
Diseases that are X-linked are transmitted by **healthy** (heterozygous) **female carriers** to males who are then affected or by **affected males** to their daughters who will be carriers. **This means that there will be a risk to the male grandchildren via their daughters.**

Fig. 8 - X-Linked Recessive Inheritance[11]

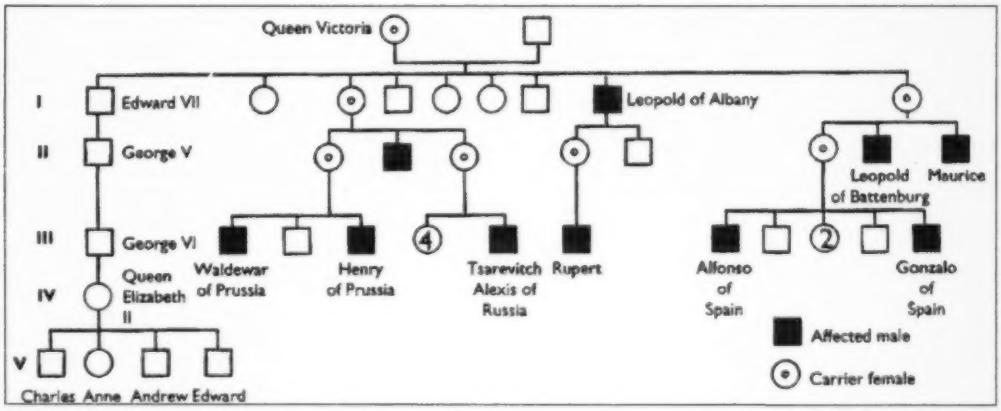
Examples of X-linked recessive disorders

- Colour blindness (red–green)
- Duchenne's and Becker's muscular dystrophies
- Fragile X syndrome
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Haemophilia A and B
- Hunter's syndrome (mucopolysaccharidosis II)

X-linked recessive inheritance



(Below) Typical pedigree for X-linked recessive inheritance, showing Queen Victoria, a carrier for hemophilia A, and her family. It shows affected males in several generations, related through females, and that affected males do not have affected sons (contrast with autosomal dominant inheritance).



The best example of this is the well known case of Queen Victoria of England. She was an unaffected carrier of the bleeding disorder known as **hemophilia**. Her daughters were unaffected but were carriers; they married into the Russian and Spanish royal families. The male offspring were affected, so that the young son of the Tsar was hemophilic.

The typical **features of X-linked recessive inheritance**:

(1) Males only are affected.

(2) Females are carriers and usually healthy.

(3) Females *might* show *mild* signs of the disease depending upon the patterns of X-chromosome inactivation (generally, only one of the two X-chromosomes in any cell is transcriptionally active – the Lyon's hypothesis).

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[11] Ibid. p. 90

(4) Each son of a *female carrier* has a 50% chance of being affected and each daughter of a female carrier has a 50% chance of being carrier.

(5) Daughters of affected males are **all** carriers.

(6) Sons of affected males are never affected because the father passes Y – chromosome to his son (i.e., there is no male-to-male transmission).

So what is the Genetic Risk?

A male transmits his X chromosome to each of his daughters and Y chromosome to each of his sons. Thus, if a male has hemophilia for instance, then has children with an unaffected (normal) female, all daughters will be unaffected but will be carriers. However, since it is on the X chromosome, none of his sons will be affected. A male cannot transmit an X-linked trait to his son(s).

Many X-linked disorders are very lethal and not compatible with survival to reproductive years.

An example of this X-linked disease is **Duchenne's Muscular Dystrophy** (DMD). It is one of the most common and severe dystrophies. In most cases, affected males are in wheelchair by age 10 – 12. Since the muscle weariness is progressive, they frequently die in their teens, before reproducing. Therefore, the disease is almost exclusively transmitted by female carriers.

Note: It is possible but extremely rare for a female to be affected by an X-linked recessive trait. Usually because they are homozygous for an X-linked condition. Again, this is relatively rare, and should not really concern us here.

Y-Linked Inheritance

Y-linked or holandric inheritance (another name for Y-linked) can only transmit the trait to his sons, not to his daughters. For the most part, this form of inheritance will have little prominence in adoption disclosures, because it affects so very few conditions. The most common is **azoospermia**.

X-Linked Dominant Inheritance

These disorders are rare but do occur. The importance of this is that female offspring and male offspring are *differently affected.* This could impact on disclosure.

Disorders can appear in both a heterozygous female, as well as in a male having a mutant allele on **his X chromosome**. This is known as **X-linked dominant inheritance**. While it initially may look like ordinary autosomal dominance because both daughters and sons, are **from an affected female**, they will have a 50% chance (1 in 2) of being affected. There is an important difference in *X-linked dominance* when compared to the *autosomal dominance*. With the X-linked type, **an affected male** transmits the trait to **all his daughters** but to **none of his sons.**

Therefore, males born to families affected by an X-linked dominant disorder are not susceptible to direct male-to-male transmission. Within a same family, there will be, however, an excess of affected females.

Some examples of this type of disorder are:

X-linked dominant **Vit-D Resistant Rickets**.
X-linked form of the **Charcot-Marie-Tooth** disease which is a hereditary motor and sensory neuropathy.

Anticipation

There are some genetic disorders that exhibit anticipation. This is when the disease appears in the offspring much *earlier than in the parents* and the disease is frequently *more severe*. It can, therefore, be a factor to consider in the decisions around disclosure. Some examples of this occur in:

- Juvenile Huntington Disease
- Fragile X syndrome
- Inherited Spinocerebellar Ataxia

Unusual Pattern of Inheritance

- Mosaicism is a condition in which a single individual possesses cells with different genotypes. It results in unusual patterns of inheritance, or unusual phenotypic features in the affected individual.
- Mosaicism can occur amongst somatic or germ cells.

Somatic mosaicism – features of a single-gene disorder but less severe than expected or it is confined to a particular body part. Ex. Neurofibromatosis type I.

Gonadal mosaicism – more common in autosomal dominant disorders, but also in some recessive disorders:

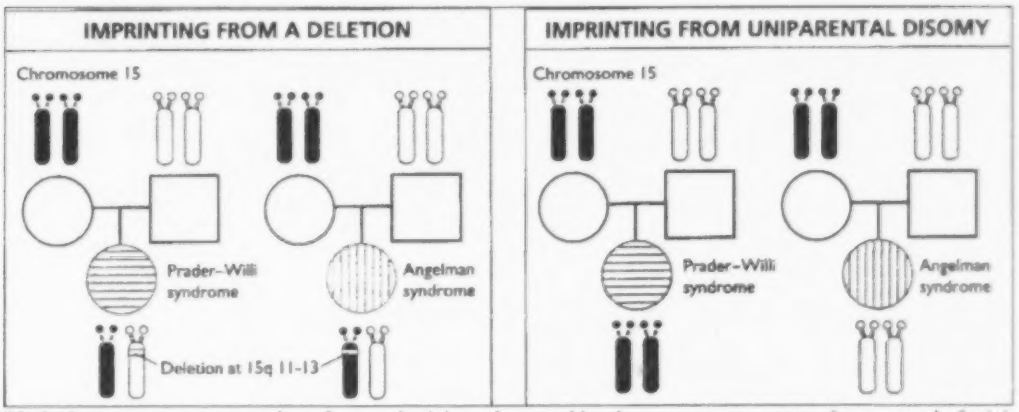
- Achondroplasia
- Osteogenesis imperfecta
- Duchenne muscular dystrophy, hemophilia and other X-linked recessive disorders.

Parent Factors:

- Genomic Imprinting: different clinical features can result depending on its origin – from the mother from the father.
- This results frequently in altered expression of a disorder.
- This is termed **genomic imprinting.** It is known to occur as two dysmorphic syndromes.
  - Prader-Willi syndrome (2% of the time)
  - Angelman syndrome (5% of the time)

These and other syndromes will be discussed in the clinical section. The diagram below shows two methods by which genomic imprinting can occur.[12]

Figure 9 **IMPRINTING**



Black chromosomes are paternal or of paternal origins, whereas white chromosomes are maternal or maternal of origin.

Genetic disorder resulting from deletion of an imprinted gene. If the deletion occurs on chromosome 15 inherited from the father, the child has Prader-Willi syndrome. If the deletion occurs on chromosome 15 from the mother, the child has Angelman syndrome.

Genetic disorder resulting from uniparental disomy affecting imprinted chromosome region. A child who inherits two maternal chromosome 15s will have Prader-Willi syndrome. A child who inherits two paternal chromosome 15s will have Angelman syndrome.

Note that regardless of the method, Prader-Willi syndrome results from a deletion on, or lack of, the *paternal* chromosome 15, while Angelman syndrome results from a deletion on, or lack of the *maternal* chromosome.

MULTIFACTORIAL DISORDERS

Multifactorial disorders are too complex to be adequately covered in this Handbook. Some comprehension, however, is necessary of this important topic, because so many common illnesses fit into this category. Many requests for disclosure will cite the genetic component as a reason for granting disclosure. Nevertheless, such a request should clearly meet the criteria set out in the beginning of page 3 of this document.

The conditions are thought to be a result of a combination of genetic susceptibility, (understood here as a predisposition to develop a certain manifestation) and the interaction of several genes (polygenic) and the environment or so-called non-genetic factors. Multifactorial inheritance accounts for several commonly encountered birth defects and a number of other important diseases with onset occurring in either early childhood or adult life.

It is important to understand that in multifactorial inheritance, the risk of recurrence (the risk of the disease re-appearing) is frequently quite low in the order of 2 – 6 %, with the greatest risk occurring in first degree relatives and rapidly decreasing as the genetic relation become more distant.

Besides the degree of relation, there are some factors that are known to increase the risk of recurrence, these are:

[12] Ibid. , p. 92

(1) Multiple affected family members.

(2) The affected proband is found more commonly among the less frequent sex. So, if there is a difference in the Male/Female ratio, the less frequent sex will be more likely to be affected.

(3) More frequent in those with disorders that are severely affected. (Ex. Individuals with bilaterally affected cleft lip and palate vs those with unilateral cleft lip).

Below are some common conditions exhibiting Multifactorial Inheritance:

Fig. 10 - Multifactorial Inheritance[13]

Congenital malformations	**Adult life**
Neural tube defects (anencephaly and spina bifida)	Atherosclerosis and coronary heart disease
Congenital heart disease	Diabetes mellitus
Cleft lip and palate	Asthma
Pyloric stenosis	Epilepsy
Congenital dislocation of the lip	Hypertension
Talipes	
Hypospadias	

Conditions with multifactorial inheritance

[13] Lissauer, T., et al. Illustrated Textbook of Pediatrics, 2nd Ed., Ibid. p. 93

CHROMOSOMAL DISORDERS

Humans have 22 pairs of autosomes and 1 pair of sex chromosomes. The term Chromosomal Disorders is discussed in greater detail below.

The Autosomal Abnormalities and Sex Chromosome abnormalities

Three autosomal trisomies are found in live born infants – others are not compatible with life. Trisomy means that three, rather than the normal two copies of a specific chromosome are present in the cells of an individual. These trisomic errors occur because of a miotic error called non-disjunction in the gamete of the mother or father. The most common trisomy and the one most people are familiar with is Trisomy 21 or Down's syndrome (see clinical section for details). Down's syndrome *risk increases with maternal age*[14], while this is not the case in the sex-chromosome disorder Turner's syndrome. Here, the incidence *does not increase with maternal age* and the recurrence rate for Turner's syndrome remains the same as the general population (see clinical section for details.)

Table 2 - Risk of Down syndrome (for live births) by maternal age at delivery

Maternal age (years)	Risk
All ages	1:700
30	1:900
35	1:380
40	1:110
44	1:37

Structural Abnormalities

There is also a group of disorders that result from altered chromosome structure that occur because of chromosome breakage, deletions, duplications, inversions and what is called unbalanced translocations. It is not necessary to understand all of the details concerning these breakages. Some common examples are shown below:

Table 3 - Chromosomal Disorders[15]

Type	Class	Name	Defect
Numerical	Autosomal	Down syndrome Edwards syndrome Patau syndrome	Trisomy 21 Trisomy 18 Trisomy 13
	Sex chromosomes	Klinefelter syndrome Turner syndrome	47, XXY 45, XO
Structural	Deletions	Prader-Willi syndrome Cri-du-chat syndrome Wilms tumour with aniridia	15q deletion 5p deletion 11p deletion

Most chromosome abnormalities occur "out of the blue" or *de novo*. They are classified as either abnormalities of number or of structure (see above), and as such may involve either the autosomes or the sex chromosomes.

[14] Pang, et al, Crash Course – Pediatrics 2nd Ed., Ibid. p. 198.
[15] Ibid. p. 197.

As noted, these disorders arise from chromosomal abnormalities with deletions being the most common type, but also duplication, inversion and unbalanced translocation. Most of these abnormalities occur *de novo* but can also arise from inheritance of an unbalanced translocation. An example of a deletion type abnormality is the **Cri-du-chat** (cry of the cat) syndrome. It is caused by a deletion to the short arm of chromosome 5 (5p-). Those children who are affected have profound mental retardation and a cat-like cry.

Some genes are 'imprinted', that is the copy derived from one parent is active, while the copy derived from the other parent is dormant (not active). Thus, when a deletion of chromosome material occurs under these circumstances it will have different effects according to which parent the deletion comes from. Thus for instance, the deletion of 15q11-13 produces different effects depending on which parent it comes from. A *paternal* origin of the deletion produces **Prader-Willi** syndrome (obesity, learning difficulties). *Maternal* origin of the deletion produces **Angelman** syndrome (happy puppet syndrome: ataxia, learning difficulties and a happy dispositions.) (Cf. pg. 18)

Mitochondrial Inheritance

Finally, there is something called Mitochondrial Inheritance. It involves mitochondrial disorders, inherited **maternally** only.

Some examples of these disorders are:

(1) Mitochondrially inherited diabetes mellitus.

(2) Mitochondrial encephalopathy, lactic acidosis, and stroke like episodes.

Mitochondrial DNA is inherited almost exclusively from the mother via her oocyte (egg); therefore, mitochondrial disorders are only inherited maternally.

- Tissues such as brain and muscle have high maternal mitochondrial representations.
- This is proposed as a possible explanation for the pattern of inheritance observed in some rare disorders, known to affect both males and females but are transmitted only through the female or by matrilineal inheritance. ex. Common in **Barth's** syndrome (endocardial myopathy)

The table below summarizes the different types of single gene or Mendelian inheritance. It should provide you with a succinct summary of the material just presented and an outline of the salient features just discussed.

Table 4 Features that support single-gene or Mendelian patterns of inheritance*	
Autosomal dominant	- Males and females are affected in equal proportions. - Affects individuals in multiple generations. - Transmission by individuals of both sexes, i.e., male to male, female to female, male to female and female to male.
Autosomal recessive	- Males and females are affected in equal proportions. - Affected individuals usually only in a single generation. - Parents are frequently related, i.e., consanguineous.
X-linked recessive	- Males are usually the only ones affected - Transmitted through unaffected females. - Males cannot transmit the disorder to their sons, i.e., no male-to-male transmission.
X-linked dominant	- Males and females affected but females are affected more often than males. - Females are less severely affected than males. - Affected males can transmit the disorder to their daughters but not to their sons.
Y-linked inheritance	- Affects males only. - Affected males will transmit the disorder/trait to their sons.

* Confer with genetic disorders classified by etiology – page 24.

SECTION I - Part II

MEDICAL AND CLINICAL GENETICS

The previous section on genetics was designed to give you the information and background to permit you to understand and assess consults, the severity of genetic conditions (ex. autosomal vs. multifactorial), and to recognize when it is appropriate to consult for further explanation and clarification.

PURPOSE OF PART II

In this section (Part II), the genetic conditions that are presented, are both the common ones and some rare ones, that might potentially prove difficult. The genetic conditions were selected because of their etiology and complexity. It should save you valuable time, and hopefully prove useful in assisting your decision making. Part II **also** describes the disorders classified by genetic type (X-linked dominant, X-linked recesssive, etc.) followed by a description and with some examples. This again provides you with models that you can compare your cases to. If for instance, you have an X-linked recessive disorder, you can compare it to the examples of X-linked recessive disorders as discussed in Part I, to get a good idea of what you are dealing with.

OR

Part III lists genetic conditions by name and specifies their **severity**. All these conditions, *unless otherwise specified*, are severe and merit a search. There is some overlap between sections of Handbook.

CAUTION:

In no way, however, is the Handbook a substitute for your good sense, nor is it meant to fetter your judgement in anyway. It is simply one of many sources you may wish to consult. Its intention is to provide you with a convenient resource.

Genetic Disorders Classified by Etiology*

Inheritance Pattern	Description	Examples
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern and females are more frequently affected than males. The chance of passing on an X-linked dominant disorder differs between men and women. The sons of a man with an X-linked dominant disorder will not be affected, but his daughters will all inherit the condition. A woman with an X-linked dominant disorder has a 50% chance of having an affected daughter or son with each pregnancy. Some X-linked dominant conditions, such as Aicardi Syndrome, are fatal to boys therefore, only girls have them (similarly Klinefelter Syndrome only occurs in boys).	• Aicardi syndrome • Hypophosphatemia
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. However, males are more frequently affected than females, and the chance of passing on the disorder differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. With each pregnancy, a woman who carries an X-linked recessive disorder has a 50% chance of having sons who are affected and a 50% chance of having daughters who carry one copy of the mutated gene.	• Colour blindness (red – green) • Duchenne's Muscular Dystrophy • Fragile X syndrome • Glucose-6-phosphate dehydrogenase deficiency (G6PD) • Hemophilia A and B • Ornithine transcarbamylase deficiency • Turner's syndrome
Autosomal Dominant	Only one mutated copy of a gene is needed for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent. There is a 50% chance that a child will inherit the mutated gene. *Many disease conditions that are autosomal dominant have low penetrance, which means that, although only one mutated copy is needed, a relatively small proportion of those who inherit that mutation go on to develop the disease,* often later in life. Examples of this include mutations on BRCA1 and BRCA2, which increase the probability of developing breast cancer, ovarian cancer, and several other cancers. In total, there are about 3,000 types of autosomal dominant disorders.	• Achondroplasia • Myotonic dystrophy • Marfan's syndrome • Neurofibromatosis type I (von Recklinghausen disease) • Tuberous Sclerosis • Huntington's Chorea • Hereditary non-Polypoid Rectal Cancers

* This part provides models for genetic patterns. For instance, you might use the description of X-linked dominant disorders as a model. It follows that **any** X-linked dominant disorder would have the characteristics of a X-linked dominant pattern.

Inheritance Pattern	Description	Examples
Autosomal Recessive	Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). Two unaffected people who each carry one copy of the mutated gene have a 25% chance with each pregnancy of having a child affected by the disorder. Total number about 1,500 types.	• Cystic Fibrosis • Congenital Adrenal hyperplasia • Inborn errors of metabolism such as phenylketonuria • Muscular dystrophy • Spinal atrophy • Tay-Sacs disease • Thalassemia* α - Thalassemia β – Thalassemia Hemoglobin H
Y-linked	Y-linked disorders are caused by mutations on the Y chromosome. Only males can get them, and all of the sons of an affected father are affected. Since the Y chromosome is very small, Y-linked disorders only cause infertility, and may be circumvented with the help of some fertility treatment.	• Male Infertility
Mitochondrial	This type of inheritance applies to genes in mitochondrial DNA. Because only egg cells can contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children. It comes then, as no surprise that this type of inheritance is also known as maternal inheritance.	• Leber's Hereditary Optic Neuropathy • Mitochondrial Diabetes Mellitus Mitochondrial Encephalopathy, Lactic Acidosis and Stroke like episodes. (MELAS)
Chromosomal	• *Autosomal type* - Trisomy 21 - Trisomy 18 - Trisomy 13 • Sex Chromosomes 47, XXY 45, XO • Structural - deletions: (i) $5p^-$ (ii) $11p^-$ • Imprinting: 15q deletion (i) Paternal (ii) Maternal	• Down's syndrome • Edward's syndrome • Patau syndrome • Klinefelter syndrome • Turner's syndrome • Cri-du-chat syndrome • Wilms Tumour with Aniridia • Prader-Willi syndrome • Angelman syndrome

* Thalassemia may not qualify – depends on severity.

Inheritance Pattern	Description	Examples
Multifactorial	Congenital malformations (i.e. Malformations present at birth). Note: This group **may** merit a search depending on severity.	• Neural tube defects • Orofacial clefts (lip and palae) • Pyloric stenosis • Talipes
Other	Common diseases: This group does **not** usually merit a search.	• Asthma • Insulin dependent diabetes mellitus (IDDM) • Hypertension
	Multifactorial psychiatric disorders are discussed in Section II of the Handbook.	• Schizophrenia • Bipolar disorders

SECTION I - PART III

THE SYNDROMES AND THEIR SEVERITY

Severity, in the clinical sense, varies along a continuum. Nevertheless, the severity of any one condition can normally be defined as being either **mild, moderate,** or **severe**. For our purposes, any condition marked as severe should merit a search; while those marked as mild should not. In addition, only those moderate conditions **that lean toward the severe side of the continuum should be granted, while those that are moderate or mild to moderate should not be considered**. Sometimes, several designations (for example: mild, moderate **and** severe) will be listed for a single condition. This means that the severity of the disorder is not consistent across individuals, and can vary along the spectrum particular of the case to properly classify it.

Developmental Genetic Conditions

Developmental abnormalities can occur for a variety of reasons, one being genetic (inherited alleles). Developmental conditions with a genetic etiology give rise to abnormalities that form in the first 12 weeks of life, as the fetus forms. By 12 weeks, all the elements that make up a recognizable fetus are present. From then on, development has more to do with growth (size, weight, etc.). Below, some of the more important developmental conditions are listed along with an indication of their severity.

Inheritance Pattern	Description	Examples
Alagille Syndrome	This is a dominantly inherited condition with a variable pattern of expression. It is due to a mutation in JAGGED1 (a protein). Individuals affected with this syndrome of arterio-hepatic dysplasia, frequently have congenital heart disease.	Moderate or severe
Gorlin Syndrome	This is a nevoid basal cell carcinoma (cancer) syndrome – comprising multiple basal cell carcinoma, odontogenic keratocyst, bifid ribs, calcification of the falx cerebri and ovarian fibromata. It is due to the Sonic Hedgehog gene (SHH). Also associated with Basal Cell Carcinoma.	Moderate to severe, severe
Lemi-Opitz Syndrome	May include abnormalities of the brain, especially holoprosencephaly (incomplete cleavage of the brain into separate hemispheres and ventricles during development). Often includes some facial and genital anomalies as well as syndactyly. This syndrome is due to a defect in the final step of cholesterol biosynthesis.	Severe
Waardenburg Syndrome, Type I	This is a syndrome is characterized by sensorial hearing loss, areas of depigmentation in the hair and skin, abnormal patterns of pigmentation in the iris and wide spaced inner canthi. It may also lead to Alveolar Rhabdomyosarcoma, an autosomal dominant disorder caused by a mutation in paired-Box (PAX) gene, in this case PAX 3.	Moderate – Severe
Waardenburg Syndrome, Type II	The more common type is the Waardenburg Type II in which the inner canthi are not widely separated and tends to be less severe. Some versions are also due to a mutation in the human microphthalmia (MITF) gene on chromosome 3.	Mild – Moderate

<table>
<tr><th>Inheritance Pattern</th><th>Description</th><th>Examples</th></tr>
<tr><td>PAX gene mutations</td><td>Developmental abnormalities associated with PAX gene mutations
<table>
<tr><th>Gene</th><th>Chromosome location</th><th>Developmental abnormality</th></tr>
<tr><td>PAX2</td><td>10q24</td><td>Renal-coloboma syndrome</td></tr>
<tr><td>PAX6</td><td>11p13</td><td>Aniridia</td></tr>
<tr><td>PAX8</td><td>2q12</td><td>Absent or ectopic thyroid gland</td></tr>
<tr><td>PAX9</td><td>14q12</td><td>Oligodontia</td></tr>
</table></td><td>Moderate – Severe
Mild
Moderate

Moderate</td></tr>
<tr><td>Campomelic dysplasia</td><td>A very rare disorder with poor long term survival. Characterized by bowing of the long bones and sex reversal in chromosomal males. It is due to a mutation of the SOX9 gene.</td><td>Severe</td></tr>
<tr><td>Holt-Oram syndrome</td><td>Characterized by congenital heart abnormalities, most notably atrial-septal defects, and upper limb radial ray reduction defects with mild hypoplasia, sometimes with duplication of the thumb to almost complete absence of the forearms. It is an autosomal dominant disorder and is characterized by a loss of function mutations in TBX 5 (T-Box gene).</td><td>Moderate – Severe, Severe</td></tr>
<tr><td>Greig syndrome and the Pallister-Hall Syndrome</td><td>The GL13 gene on chromosome 7 containing the zinc-finger motif, has been thought to cause both these syndromes. This motif acts as a transcription factor by binding the zinc-finger to DNA.

The Greig syndrome is characterized by cephalo-polysyndactyly (head, hand and foot abnormalities). The Pallister-Hall syndrome results from frame-shift mutation and presents with polydactyly, hypothalamic hamartoma and an imperforate anus.</td><td>Moderately severe</td></tr>
<tr><td>Denys-Drash syndrome & Wilms' Tumour</td><td>Also a zinc-finger related gene, WT1 on chromosome II causes Wilms Tumour and Denys-Drash syndrome, in which the external genitalia are ambiguous and there is progressive renal failure.</td><td>Severe</td></tr>
<tr><td>Hirschsprung Disorder</td><td>Produced as a result of the proto-oncogene RET on chromosome 10q11.2. Some 50% of Hirschsprung disease cases, in which there is failure of migration of ganglionic cells to the submucosal and mesenteric plexus of the large bowel. Usually seen shortly after birth with abnormal distention and intestinal obstruction.</td><td>Moderate, Moderate to Severe</td></tr>
</table>

Inheritance Pattern	Description	Examples
Pfeifer 8p11	A syndrome caused by a mutation to the gene for Fibroblast Growth Factor Receptors (FGFRs). Presents with abnormalities of thumb and/or big toe.	Moderate, Moderate to Severe
Apert syndrome 10q25	Also a FGFR2 related origin. It is characterized by craniosynostosis, and abnormalities of the hand and foot, especially syndactyly.	Moderate, Moderate to Severe
Crouzon syndrome 10q25	FGFR2 related syndrome, characterized by Achondroplasia and Hypochondroplasia All are due to FGFR3 on 4p16. These involve some form of dwarfism.	Moderate to Severe
Thanatophoric dysplasia	Note: Thanatophoric dysplasia is ultimately a lethal skeletal dysplasia.	Severe
DiGeorge syndrome also called – Velocardiofacial syndrome	Although it may appear to be autosomal dominant, DiGeorge syndrome is actually a chromosomal disorder, affecting 1 in every 4,000 births. It is characterized by numerous cardiac abnormalities especially of the outflow tract. Thymic and parathyroid hypoplasias are also common. The gene TBX1, may actually be responsible for the syndrome which results from submicroscopic chromosome deletion of band 22q11.	Severe

The next section deals with Blood (haematological) genetic syndromes.

Inheritance Pattern	Description	Examples
Sickle-Cell Disease	• Autosomal recessive. Presents with any or all of: cerebral symptoms, kidney failure, pneumonia, heart failure, weakness and lassitude. • Caused by a mutant allele. Important for a client/relatives to know their sickle-cell status, especially for conception. This condition **should always merit a search.**	Mild; moderate, severe
Sickle-Cell Trait	All of the same consideration as above – **should merit a search**, even if client seems unaffected, and is an exception to the severity rule.	Mild, moderate
α Thalassemia	An inherited disorder, which particularly affects Middle Eastern and Mediterranean peoples. There are several forms of Thalassemia, but only two types – one severe and one mild – are common. Since α Thalassemia is so heterogeneous in nature, it **should always merit a search.**	Mild - Severe

Inheritance Pattern	Description	Examples
β Thalassemia	Persons who are homozygous for β thalassemia have severe transfusion dependent anemia. It is caused by a wide variety of different mutations.	Severe
Cooley's Anemia	Most severe form of β-thalassemia, Cooley's anemia, usually presents itself in the first year of life. Unless treated, distortions of the face and skull can occur. • Patients use to die in their 20's as a result of iron overload. Now treatable. **All patients with Thalassemia should merit a search.**	Severe

Immunodeficiency Disorders. These disorders are uncommon but usually severe.		
Inheritance Pattern	**Description**	**Examples**
Chronic Granulomatous disease	Inherited as either an autosomal recessive disorder or as an X-linked disorder. Presents with an inability to resist infections and is associated with high childhood mortality.	Severe
Leukocyte Adhesion disorder	A fatal disorder unless antibiotics are given until a bone marrow transplant can be performed. - often X-linked or autosomal recessive.	Severe
Bruton-type Agamma-globulinemia	It is a life threatening condition with high mortality. It is a deficiency of immunoglobulin and B-cell lymphocytes.	Severe
Hyper-1gM syndrome	X-linked recessive disorder marked by elevated 1gM and usually 1gD. Individuals are susceptible to life-threatening pyogenic infections.	Severe
Severe combined Immunodeficiency (SCID)	SCID is generally heterogenous and can be inherited as either an X-linked recessive or as an autosomal recessive disorder. Individuals are susceptible to both viral and bacterial infection. Death usually occurs in infancy unless a bone marrow transplant is performed. Very few have survived into adulthood.	Severe

Inheritance Pattern	Description	Examples
Ataxia Telangiectasia	An autosomal recessive disorder presenting in early childhood. Affected individuals have great difficulty controlling their movements and balance. They also show pronounced conjunctiva and oculocutaneous telangiectasia and are susceptible to sinus and pulmonary infections.	Severe
Wiskott-Aldrich syndrome	X-linked recessive disorder. Affected individuals (predominantly boys) have eczema, diarrhea, recurrent infections, a low platelet count (thrombocytopenia) and usually a low serum 1gM, impaired T-cell function. Until recently, most affected individuals died in their teens. Now bone marrow transplant can save some.	Severe

MALIGNANT SYNDROMES WITH GENETIC LINKS

The three tables that follow briefly describe a number of cancers that are genetic. All cancers are obviously serious, but from an adoption-disclosure perspective, those with a strong genetic component have significance for siblings and 1st degree relatives. **Because of this genetic link, you will want to grant a search in these cases because of this genetic link.**

Burkitt Lymphoma	Prevalent among Africans. Presents as a lymphoma of the jaw. 90% of affected children have a translocation of the c-MYC oncogene of the long arm of chromosome 8, to the heavy chain (H) immunoglobulin locus on chromosome 14 (less commonly of chromosome 3 to chromosome 22).	Severe
Retinoblastoma	Relatively rare, highly malignant childhood tumour of the eye (retinal cells). There are three forms: - an autosomal dominant and non-hereditary - good prognosis if treated early - Due to tumour suppressor mutations in gene RB1 with a locus at 13_q14	Severe

There are other cancers like the retinoblastoma. There are so called familial cancers, with a high probability of being parred on from generation to generation. These include some we have or will discuss such as breast (BRCA2 with 13q12-13 locus), Wilms tumour (WT1 with locus 11p13) but there are others such as Familial adenopolyposis (APC, 5q31), Li-Fraumeni syndrome (Tp53, 17q13), Breast-Ovarian CA (BRACA2, 17q21), Gastric cancer CDH, and colorectal cancers (RAS gene, Tp53 and LOH on 5q and 18q).

Syndromes and Cancers that show loss of heterozygosity and their chromosomal location[16]

Syndrome or Cancer	Chromosomal Location
Retinoblastoma	13q14
Osteosarcoma	13q, 17p
Wilms' tumor	11p13, 11p15, 16q
Renal carcinoma	3p25, 17p13
von Hippel-Lindau disease	3p25
Bladder carcinoma	9q21, 11p15, 17p13
Lung carcinoma	3p, 13q14, 17p
Breast carcinoma	11p15, 11q, 13q12, 13q12, 13q14, 17p13, 17q21
Rhabdomyosarcoma	11p15, 17p13
Hepatoblastoma	5q, 11p15
Gastric cancer	1p, 5q, 7q, 11p, 13q, 17p, 18p
Familial adenomatous polyposis	5q21
Colorectal carcinoma	1p, 5q21, 8p, 17p13, 18q21
Neurofibromatosis I (NF1 von Recklinghausen disease)	17q
Neurofibromatosis II (NF2)	22q
Meningioma	22q
Multiple endocrine neoplasia type 1 (MEN 1)	11q
Thyroid medullary carcinoma	1p
Pheochromocytoma	1p
Melanoma	9p21, 17q
Ovarian Cancer	11q25, 16q, 17q
Pancreatic Cancer	9p21, 13q14, 17p13
Prostate cancer	1p36, 7q, 8p, 10q, 13q, 16q

Some familial cancers or cancer syndromes due to tumors suppressor mutations[17]

Disorder	Gene	Locus
Retinoblastoma	*RBI*	13q14
Familial adenomatous polyposis	*APC*	5q31
Li-Fraumeni syndrome	*Tp53*	17p13
von Hippel-Lindau syndrome	*VHL*	3p25-26
Multiple endocrine neoplasia type II	*RET*	10q11.2
Breast-ovarian cancer	*BRCA1*	17q21
Breast cancer	*BRCA2*	13q12-13
Gastric cancer	*CDH1*	16q22.1
Wilms tumor	*WT1*	11p13
Neurofibromatosis I	*NF1*	17q12-22

[16] Turnpenny, Peter; Ellard, Sian: Emery's Element of Medical Genetics, 12th Ed., Elsevier Churchill Livingstone, 2005, p. 212.
[17] Ibid. p. 215

Inherited family cancer syndromes, mode of inheritance, gene responsible and chromosomal site.[18]

Syndrome	Mode of inheritance*	Gene	Chromosomal site	Main cancer(s)
Breast/ ovary families	AD	*BRCA1*	17q21	Breast, ovary, colon, prostate
Breast families	AD	*BRCA2*	13q12	Breast, ovary
Familial adenomatous polyposis	AD	*APC*	5q21	Colorectal, duodenal, thyroid
Turcot's	AD	*APC* *hMLH1* *hMSH2*	5q21 3p21 2p15-16	Colorectal, brain
Hereditary non-polyposis colorectal cancer (HNPCO)				
• Lynch I	AD	*hMSH2* *hMSH6* *hMLH1* *hPMS1* *hPMS2*	2p15-16 2p15-16 3P21 2q31 7p22	Colorectal
• Lynch II	AD	*hMSH2* *hMLH1* *hPMS1* *hPMS2*	2p15-16 3p21 2q31 7p22	Colorectal, endometrial, urinary tract, ovarian, gastric, small bowel, hepatobiliary
MYH polyposis	AR	*MYH1p33*		
Muir-Torre	AD	*hMSH2*	2p15-16	Same as Lynch II plus sebaceous tumors, laryngeal
Juvenile polyposis	AD	*SMAD4/DPC4* *BMPR1A*	18q21.1 10q22	Colorectal
Peutz-Jeghers	AD	*STK11*	19p13.3	Gastrointestinal, breast, uterus, ovary, testis.
Cowden disease	AD	*PTEN*	10q23	
Familial retinoblastoma	AD	*RB1*	13q14	Retinoblastoma
Li-Fraumeni	AD	*Tp53*	17p13	Sarcoma, breast, brain, leukemia, adrenal cortex
Multiple endocrine neoplasia (MEN)				
Type I (MEN1)	AD	*MEN1*	11q13	Parathyroid, thyroid, anterior pituitary, pancreatic islet cells, adrenal
Type II (MEN2)	AD	*RET*	10q11.2	Thyroid (medullary), pheochromocytoma
von Hippel-Lindau	AD	*VHL*	3p25-26	CNS hemangioblastoma, renal, pancreatic, pheochromocytoma
Gorlin (nevoid basal cell carcinoma) syndrome	AD	*PTCH*	9q22	Basal cell carcinomas, medulloblastoma, ovarian fibromas, (odontogenic keratocysts)
Dysplastic nevus syndrome	AD	*CMM1*	1p	Melanoma (familial atypical mole melanoma, FAMM)

[18] Ibid. p. 219

OTHER CANCERS WITH A KNOWN GENETIC COMPONENT

It is believed that at least 5% of all colorectal cancers and breast cancers result from cancer susceptibility genes. There are similar findings for many other cancers as well. We have already discussed some of these like Neurofibromatosis I, Wilms Tumor, and Retinoblastoma. The following is a list of some **familial cancers** (frequently due to something called Tumour Suppressor Mutations. Three of these, although rare, have required consults in the past – von Hippel-Lindau syndrome, Li-Fraumeni syndrome and familial adenomatous polyposis.

Inheritance Pattern	Description	Examples
Von Hippel-Lindau syndrome	Presents with central nervous system (CNS) hemangioblastoma, renal, pancreatic, pheochromocytoma.	Severe
Familial adenomatous polyposis	• An autosomal dominant disorder. • Affected individuals have multiple polyps of the large bowel, with occurrence of CA of the colon.	Severe
Li-Fraumeni syndrome	• Autosomal dominant trait. • Affected individuals are very susceptible to many forms of cancer, especially sarcomas, adrenal carcinoma, and breast cancer.	Severe
Cowden Disease	• Autosomal dominant disorder. • Affected individuals have a greater than 50% incidence of breast cancer (from a young age) and about 7% develop papillary thyroid disease.	Severe
Peutz-Jegher syndrome	• Autosomal dominant disorder. • Dark melanin spots on the lips, around the mouth, on the palms and plantar areas as well as on other extremities. • Individuals with the disorder get multiple polyps in the small intestine. There are hamartomas with a significant risk of malignant transformation. There is also a great risk of cancers at other sites – breast, uterus, ovary, testes occurring early in adult life.	Moderate to Severe

The Two Important "Female" Cancers		
Inheritance Pattern	**Description**	**Examples**
Ovarian Cancer	1 in 70 women develop ovarian cancer, the incidence increasing with age. 5% of the women with ovarian cancer have a familial history. 1% of these follow a dominant inheritance pattern. Mortality is very high. • Ovarian cancer is associated with the BRCA2 gene.	Severe
Breast Cancer	1 in 12 women in Western society develop breast cancer. It is the most common cancer in women between 40 and 55 years of age, with 1 in 3 women with breast cancer going on to develop **metastatic disease**. 15-20% of the breast cancers is due to a familial transmission. • The tendency to develop breast cancer is strongest in those who carry the BRCA1 gene on the long arm of chromosome #17. • See Lifetime Risk chart on the next page.	Severe
The Male Cancer		
Prostate Cancer	One out of every ten men will develop prostate cancer, and 3% will die from it. • Those with a 1st degree relative have a 2-5 times greater risk of developing the disease at an earlier age. • Age of onset is the main indicator here. Those with early onset or a first degree relative with cancer of the prostate should be considered for a search.	Moderate to Severe

The following two tables present the lifetime risk of developing breast cancer and colorectal cancer in those with family history of these cancers.

Lifetime risk of breast cancer in females according to the family history of breast cancer.[19]

Population risk	1 in 12
Sister diagnosed 65–70 years of age	1 in 8
Sister diagnosed under 40 years of age	1 in 4
Two first-degree relatives affected under 40 years of age	1 in 3

Lifetime risk of colorectal cancer in individuals according to the family history of colorectal cancer[20]

Population risk	1 in 50
One first-degree relative affected	1 in 17
One first-degree relative and second-degree relative affected	1 in 12
One relative aged under 45 affected	1 in 10
Two first-degree relatives affected	1 in 6
Three or more first-degree relatives affected	1 in 2

From Houlston RS, Murday V. Harocopos C, Williams C B, Slack J 1990 Screening and genetic counselling for relatives of patients wit colorectal cancer in a family screening clinic. Br Med J 301: 366-368.

[19] Ibid. p. 220
[20] Ibid. p. 220

DYSMORPHIC SYNDROMES

These syndromes are a result of either genetics or abnormal development (something goes wrong in the developmental process, although the genetics are normal – these are termed malformations. These are discussed more fully in the medical section. Only those with a clear genetic basis are considered here.

Inheritance Pattern	Description	Examples
	Below is a list of congenital abnormalities caused by a **single gene** defect. These tend to involve only one organ system. They may be mild or severe depending on which organ system is involved.	
Hydrocephalus (CNS)	Sex linked, central nervous system defects, characterized by a large head, with enlarged ventricles. Usually requires a shunt from the brain to keep normal pressure. Intelligence can be normal or abnormal. Hydrocephalus is a life threatening condition – early diagnosis is, therefore, crucial.	Severe
Megacephaly	Megacephaly (large head) is an autosomal dominant disorder. Its impact is variable, therefore, will **need a consult** to decide if it should be granted.	Variable ↓ **Needs a consult**
Microcephaly	Microcephaly (small head) is caused by either autosomal dominant or autosomal recessive genes; it is variable in its expression and **needs a consult.**	Variable ↓ **Needs a consult**
Syndromes Apert	Autosomal dominant disorder with craniosynostosis and syndactyly.	Mild to severe
EEC	Autosomal dominant: with ectodermal dysplasia, cleft lip and palate.	Moderate to severe
Mechel	Autosomal recessive disorder with encephalocele polydactyly and polycystic kidneys.	Severe
Roberts	Autosomal recessive disorder with cleft lip and palate and phocomelia.	Moderate to severe
Van der Woude	Autosomal dominant disorder with cleft lip/palate and lip pits.	Moderate to severe

Inheritance Pattern	Description	Examples
Noonan Syndrome	Single gene disorder with an abnormality at the 12q22 locus. Similar to Turner's syndrome – short stature, neck webbing, increased carrying angle at the elbow, congenital heart disease, pulmonary stenosis, sometimes ASD or VSD and more rarely hypertrophic cardiomyopathy.	Severe
Sotos syndrome	The single gene disorder, either by balanced chromosome translocation at 5q35 or by deletion of gene NSD1. Also referred to as cerebral gigantism. Affected individuals present with advanced bone age, enlarged cerebral ventricles (though usually mild), high prominent forehead, hypertelorism, downward slanting palpebral fissures and long pointed chin and often with severe learning disabilities. May need a consult but **if most of the above characteristics are present, grant the search**.	Mild/ moderate/ severe
Huntington's Chorea or Disease	An autosomal dominant disorder. One of the worst inherited diseases. Marked by progressive neurological disability. Its course usually takes about 15 years and beginnings in one's 40s. There are intellectual and psychiatric disturbances. Chorea form movements and ataxia are common symptoms. Eventually dementia and death follow.	Severe
Myotonic Dystrophy	Autosomal dominant disorder. Myotonic dystrophy is the most common form of muscular dystrophy. With an incidence of 1 in 8,000. An early onset form can occur, it is exclusively passed on by the mother; and in contrast, the juvenile form is a milder and generally passed on from the father. Both forms are characterized by a progressive weakness and myotonia, as well as possible cataracts, cardiac conduction abnormalities, dysphagia, constipation, and incontinence. Respiratory distress is life threatening.	Severe
Charcot-Marie-Tooth syndrome	Autosomal dominant disorder, occasionally recessive. This is a hereditary motor-sensory neuropathy. Characterized by symmetrical, slowly progressive muscle wasting. • **Seek a consult for this disorder.**	Mild to Moderate ↓ **Seek consult**

Inheritance Pattern	Description	Examples
Marfan's syndrome	Autosomal dominant disorder linked to the FBN1 gene on chromosome 15q21. This fibrous connective tissue disorder is characterized by skeletal, ocular and cardiovascular manifestation as well as a predisposition to spontaneous pneumothorax. Pregnancy is a very great risk factor for women. Also, cardiac abnormalities may be substantial. Although symptoms can be mild to severe, cardiac **risk factors warrant that a search be granted.**	Mild/ Moderate to Severe
Cystic Fibrosis	An autosomal recessive disorder, characterized by the presence of very viscus mucous. In 1955 life expectancy was 5 years – today it is 37.5 years. CF should be considered a serious life threatening disease.	Severe
Werdnig-Hoffmann disease	Autosomal recessive inheritance. While not compatible with life beyond 2 years of age, a search **should be granted to** carriers of this disease.	Severe
Kugelberg-Welander disease	An autosomal recessive disorder marked by slow progressive muscle weakness - wheelchair bound by adult life. High mortality rate due to respiratory infections and failure.	Severe
Williams syndrome	A chromosomal disorder caused by microdeletion and characterized by short stature, facial abnormalities, transient neonatal hypercalcemia, and congenital heart disease – supravalvular aortic stenosis. Affected individuals are all learning disabled.	Moderate to Severe
Smith-Magenis syndrome	A microdeletion syndrome (with loss of chromosome material at 17p.11.2) characterized by congenital heart disease (in 1/3 of all cases), scoliosis and hearing impairment.	Severe
Turner's syndrome	There is only one x chromosome (XO). Incidence is 1:2,500. Varying chromosomal abnormalities can be found 45X0, 45, XO/46, XY. **This condition requires a consult.**	Mild/ moderate
Fragile X	Characterized by a number of physical problems but the main impact is intellectual. Presents with learning difficulties – moderate to severe. It mainly affects males but females can be carriers. **Should consider a consult for this syndrome.**	Moderate to Severe

	INBORN ERRORS OF METABOLISM	
Inheritance Pattern	**Description**	**Examples**
	Over **200 inborn errors of metabolism are known**. A summary chart is given at the end of this chapter which summarizes the most commonly encountered ones. What follows here are some of the more prominent disorders, ones you are likely to encounter, or ones which, while not common, are severe. Most all inborn errors of metabolism are autosomal recessive or X-linked pattern of inheritance. Only a few are autosomal dominant.	

DISORDERS OF THE AMINO ACIDS

Phenylketonuria (PKU)	The most common amino acid disorder is Phenylketonuria or PKU. If left untreated at birth, it will result in severe mental retardation and convulsions.	Severe
Alkaptonuria	An autosomal recessive disorder. Generally not life threatening; results in the deposition of a dark pigments in body tissues and joints, and frequently leads to arthritis. **Persons with this disorder do not need to have a search, as they do not meet the definition of severe.**	Mild
Homocystinuria	It is a recessively inherited inborn error of metabolism. It is characterized by mental retardation, fits, osteoporosis, thromboembolic episodes, and a tendency for dislocation of the lens.	Severe
Maple Syrup Disease	• Autosomal recessive disorder. • Characterized at birth by vomiting, and alternating increased/decreased tone, proceeding to death in a few days if not recognized and treated. • Mental retardation	Severe
Oculocutaneous Albinism	• Autosomal recessive disorder • Caused by a deficiency of Tyrosinase • Lack of skin and hair pigment as well as eye defects.	Severe

UREA CYCLE DISORDERS		
Inheritance Pattern	**Description**	**Examples**
	• The urea cycle is a five-step metabolic pathway (primarily occurring in liver cells) for the removal of waste (**nitrogen** from the amino acid groups, arising from the normal breakdown of protein.) • A deficiency of enzymes implicated in the urea cycle results in an intolerance to protein due to the accumulation of ammonia in the body – **hyperammonemia.**	
Carbamyl synthetase deficiency	• Autosomal recessive disorder • Hyperammonemia – coma and/or death	Severe
Ornithine carbamyl transferase	• X-linked dominant disorder • Hyperammonemia – death in early infancy	Severe
Citrullinemia	• Autosomal recessive disorder • Argininosuccinic acid synthetase • Variable clinical causes	Needs consult
Argininosuccinic Aciduria	• Autosomal recessive disorder • Argininosuccinic acid lyase • Hyperammonemia, mild mental retardation, and protein intolerance.	Moderate to severe; needs consult.
Hyperargininemia	• Autosomal recessive disorder • Arginase deficiency • Hyperammonemia, progressive spasticity, and intellectual deterioration.	Severe

	DISORDER OF CARBOHYDNATE METABOLISM	
Inheritance Pattern	**Description**	**Examples**
	These inborn errors of metabolism can be divided into **two main groups: disorders of monosaccharide metabolism and the glycogen storage disorders**. Glycogen storage disease also has a sub-division that primarily affects muscle.	
Group I: Monosaccharides	Two subtypes exist: • Galactosemia deficiency • Hereditary fructose intolerance	
Galactosemia	• Autosomal recessive disorder • Deficiency of galactose-1-phosphate uridylyl transferase. • cataracts, mental retardation and cirrhosis.	Severe
Hereditary fructose intolerance	• An autosomal recessive disorder • Deficiency of fructose-1-phosphate aldolase • Failure to thrive, vomiting, jaundice, convulsions.	Severe
Group II: Glycogen Storage Diseases (GSD)	**Group II GSDs** primarily affect the **liver** 4 subtypes exist: • Von Gierke Disease (GSDI) • Cori Disease (GSD III) • Andersen Disease (GSD IV) • Hepatic phosphorylase deficiency (GSD VI)	
Von Gierke Disease (GSDI)	• Autosomal recessive disorder • Glucose-6-phosphatase • Hepatomegaly, hypoglycemia, sweating, tachycardia. **In spite of its mild presentation, a search should be granted as knowledge of its existence leads to a more rapid diagnosis and treatment.**	Moderate
Cori Disease (GSD III)	• Autosomal recessive disorder • Amylo-1, 6-glucosidase • Infants present with hepatosplenomegaly Knowledge of potential inheritance important for early diagnosis and treatment, therefore, **a search should be granted.**	Moderate

Inheritance Pattern	Description	Examples
Andersen Disease (GSD IV)	• Autosomal recessive disorder • Glycogen brancher enzyme deficiency • Liver failure and/or death	Severe
Hepatic Phosphorylase deficiency (GSD VI)	• Can follow either an autosomal recessive or an X-linked inheritance pattern. • Failure to thrive, hepatomegaly, and hypoglycemia • **Early diagnosis is crucial to treatment – a search should be granted.**	Moderate
Group III	Glycogen Storage Disease • Primarily affects muscle • Pompe disease (GSD II) • McArdle's disease (GSD V)	
Pompe Disease (GSD II)	• Autosomal recessive disorder • Lysosomal α–1, 4-glucosidase. • Floppiness, heart failure, and death.	Severe
McArdie (GSD V)	• Autosomal recessive disorder • Muscle phosphorylase • Muscle cramps • **Does not meet the test of severity.**	Mild
	DISORDERS OF STEROID METABOLISM • Mostly inborn **errors of steroid metabolism in the biosynthetic pathways of CORTISOL.** • These can result in the virilization of female fetuses, along with associated salt loss in both affected males and females due to a deficiency of aldosterone. In addition, these disorders may involve the androgen receptor defects, virilization of chromosomally male individuals.	
Congenital adrenal hyperplasia	• Autosomal recessive disorder caused by an abnormality at chromosome 6. • 21 hydroxylase, 11 β hydroxylase, and 3-β hydroxylase. • Virilization, salt losing enteropathy. • Volume depletion, electrolyte imbalance, death.	Severe
Androgen Insensitivity Syndrome (AIS)	• X-linked recessive disorder • Female external genitalia, testes, male chromosomes.	Severe

	DISORDERS OF LIPID METABOLISM	
Inheritance Pattern	**Description**	**Examples**
	Familial hypercholesterolemia is the commonest autosomal dominant single-gene disorder in Western society.	
Familial Hyper-cholesterolemia	• Autosomal dominant • Low density lipoprotein receptor • Early coronary artery disease	Mild to Moderate
	MUCOPOLYSACCARIDOSES DISORDERS (MPSs)	
	• **Parents with skeletal, vascular or Central Nervous System (CNS) abnormalities.** • These symptoms result from a progressive accumulation of sulphate polysaccharides (also known as glycosaminoglycans) in the body. Degradation of the carbohydrate side-chains of Acid Mucopolysaccharide. • Each specific MPS has a characteristic excretion in the urine, namely: glycosaminoglycans, dermatan, heparan, keratan, or chondroitin sulphate. • All but Hunter syndrome, which is X-linked, are inherited as **autosomal recessives**.	
Hurler Syndrome (MPS I)	• Autosomal recessive disorder • α –L-iduronidase • Marked by mental retardation, skeletal abnormalities, hepatosplenomegaly and corneal clouding.	Severe
Hunter Syndrome (MPS II)	• X-linked recessive disorder • Iduronate sulphate sulphatase • Marked by mental retardation, skeletal abnormalities and hepatosplenomegaly.	Severe
Sanfilippo Syndrome (MPS III)	• Autosomal recessive disorder • Behavioural problems, dementia and fits • Heparin-S-Sulphaminidase (MPS IIIA) • N-ac-α-D-glucosaminidase (MPS IIIB) • Ac-CoA-α-glucosaminidase-N-acetyltransferase (MPS IIIC) • N-Ac-glucosamine-6-sulphate sulphatase (MPS IIID). • Behavioral problems, dementia and fits.	Severe

Inheritance Pattern	Description	Examples
Morquio Syndrome (MPS IV)	• Autosomal recessive disorder • Galactosamine-6-sulfatase (MPS IV A) • B-galactoside (MPS IV B) • Corneal opacities, short stature, and skeletal abnormalities.	Severe
Maroteaux-Lamy Syndrome	• Autosomal recessive disorder • Arylsulphatase B, N-acetyl-galactosamine • Corneal clouding, skeletal abnormalities, and cardiac abnormalities.	Severe
Sly Syndrome	• Autosomal recessive disorder • B-glucuronidase • Variable penetration of skeletal and cardiac abnormalities, corneal clouding, and mental retardation.	Severe
	OTHER LIPID STORAGE DISEASES (SPHINGOLIPIDOSES)	
	• These disorders characterized by an inability to degrade sphingolipids. This results in the progressive deposition of lipids or glycolipid, primarily in the **brain, liver** and **spleen**.	
Tay-Sachs Disease	• Autosomal recessive disorder • Hexosaminidase-A deficiency • Developmental regression, blindness, a cherry-red spot, and deafness. • Tay-Sachs disease particularly affects those of European Jewish ancestry (Ashkenazi)	Severe
Gaucher Disease	• Autosomal recessive disorder. • There are two types: Type I: - joint and limb pain plus splenomegaly - due to a deficiency in glucosylceramide Type II: - spasticity fits, death - due to a deficiency in β-glucosidase	Severe

Inheritance Pattern	Description	Examples
Niemann-Pick Disease	• Autosomal recessive disorder • Sphingomyelinase deficiency • Failure to thrive, hepatomegaly, cherry-red spot, developmental regression.	Severe

	DISORDERS OF PURINE AND PYRIMIDINE METABOLISM	
Lesch-Nyhan Disease	• X-linked recessive disorder • Hypoxanthine-guanine-phosphoribosyltransferase • Mental retardation, uncontrolled motor movements and self-mutilation.	Severe
Adenosine deaminase deficiency	• Autosomal recessive disorder • Adenosine deaminase deficiency • Can cause severe Combined Immuno Deficiency with impaired T and B lymphocytes. • Require a bone marrow transplant.	Severe
Purine Nucleoside Phosphorylase	• Autosomal recessive disorder • Deficiency of purine nucleoside phosphorylase • Susceptible to severe (life threatening) viral infections due to impaired T-cell function.	Severe
Hereditary Orotic Aciduria	• Autosomal recessive disorder • Orotate phosphoribosyl transferase and orotidine 5 (-phosphate decarboxylase) • Megablastic anaemia, failure to thrive, and developmental delay.	Moderate – Severe

	DISORDER OF PORPHYRIN METABOLIS	
Inheritance Pattern	**Description**	**Examples**
	• The different types of porphyrias are associated with neurological, visceral or cutaneous manifestations of disease due to an accumulation of different porphyrin precursors in the respective organs. • The porphyrias are divided into two types depending on whether the excess production of porphyrins occurs predominantly in the liver or in the erythropoietic system. **Other than for congenital erythropoietic porphyria which is autosomal recessive, all the others in this group are autosomal dominant.**	
Group I: Hepatic Porphyrias	• Mainly excessive production occurs in the liver.	
Acute intermittent porphyria (AIP)	• Uroporphyrinogen 1 synthetase • Abdominal pain, CNS effects	Severe
Hereditary Coproporphyria (HCP)	• Autosomal dominant disorder • Coproporphyrinogen oxidase • Abdominal pain, CNS, photosensitivity	Severe
Porphyria Variegata (VP)	• Autosomal dominant disorder • Protoporphyrinogen oxidase • Photosensitivity, CNS, abdominal pain	Severe
Group II Erythropoietic Porphyrias	• Mainly affects erythropoietic systems.	
Congenital Erythropoietic Porphyria	• **Autosomal recessive disorder** • Urobilinogen III synthase • Hemolytic anaemia and/or photosensitivity • **This condition does not generally meet the definition of severe under the legislation.**	Moderate

Inheritance Pattern	Description	Examples
Erythropoietic Protoporphyria	• Autosomal dominant disorder • Ferrochelatase • Photosensitivity and liver disease (may be severe) • Judge on a case-by-case basis.	Moderate - Severe
	ORGANIC ACID DISORDERS • Tend to be episodic, parenting with poor feeding, vomiting, lethargy and severe metachrotic acidosis (may lead to death).	
Methylmalonic Acidemia	• Autosomal recessive disorder • Methylmalonyl-CoA mutase • Hypotonia, poor feeding, acidosis, and development delay	Severe
Propionic Acidemia	• Autosomal recessive disorder • Propionyl-CoA carboxylase deficiency • Poor feeding, failure to thrive, vomiting, acidosis, and hypoglycemia	Severe

	DISORDER OF COPPER METABOLISM There are only two major inborn errors of metabolism to copper: 1. Menkes Disease 2. Wilson Disease	
Menkes Disease	• X-linked recessive disorder • ATP are members of the copper deficiency group • Failure to thrive, and neurological deterioration • Transport protein deficiency	Severe
Wilson Disease	• Autosomal recessive order • ATP are members of the copper deficiency group • Spasticity, rigidity, dysphagia, and cirrhosis • Transport protein deficiency	Severe

	PEROXISOMAL DISORDERS	
Inheritance Pattern	**Description**	**Examples**
	The peroxisomes are subcellular organelles with a trilayer lipid membrane present in all cells. • Carry out a number of reactions involved in fatty acid oxidation and cholesterol biosynthesis interacting with metabolic pathways outside the peroxisomes. There are two main categories of Peroxisomal disorders: (1) Those characterized by a reduced number of all types of peroxisomes (as in Zellweger syndrome) (2) Those with a deficiency of a single isolated peroxisomal enzyme (as is the cases with X-linked adrenoleuko-dystrophy).	
Zellweger Syndrome	• Autosomal recessive disorder • All the peroxisomal enzymes affected • Dysmorphic features, hypotonia, enlarged liver, and renal cysts. • Frequent fits, may die early.	Severe
Adrenoleuko-Dystrophy	• X-linked recessive disorder • High level of Very Long-Chain Fatty Acid (VLCFA) – CoA synthetase. • Mental deterioration, fits, behavioral changes, adrenal failure. • Must be assessed on a case-by-case basis – may even be asymptomatic.	Mild, Moderate or Severe

	MITOCHONDRIAL DISORDERS	
	Symptoms generally include mitochondrial with encephalopathy, dementia, ataxia, dystonia, neuropathy seizures and myopathic fits.	
MERRF	• Mitochondrial disorder • Results from a mutation in lysine to RNA with G>A 8344 substitution and T>C 8356 substitution. • Myoclonus, seizures, optic atrophy, and hearing impairment	Severe

Inheritance Pattern	Description	Examples
MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes)	• Mitochondrial disorder • Mutation in leucine tRNA-3243G • Encephalopathy, stroke like episodes, seizures, dementia, migraine, and lactic acidosis	Severe
Leigh Disease	• Mitochondrial disorder • Mutation in subunit 6 to ATP are (usually) T>G 8993 substitution – NARP mutation • Marked by hypotonia, psychomotor regression, ataxia, and spastic quadriparesis	Severe
Leber Hereditary Optic Neuropathy	• Mitochondrial disorder • Caused by a mutation in ND1, ND4, ND6, or 11778A • Symptoms include retinal regression, and occasionally cardiac condition defects	Severe
Barth Syndrome	• X-linked recessive disorder • Uncertain. Deficit is not fully identified as of yet • Cardioskeletal myopathy, growth retardation and neutropenia	Severe
	DISORDERS OF FATTY ACID OXIDATION These disorders are associated with skeletal weakness, abnormal muscle fatty-acid metabolism and decreased muscle connection.	
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	• Autosomal recessive disorder • Episodic hypo ketogenic hypoglycemia dehydrogenase	Moderate to Severe
Glutaric aciduria Type I	• Autosomal recessive disorder • Glutaryl-CoA dehydrogenase • Episodic encephalopathy and cerebral palsy-like dystonia	Severe
Glutaric Aciduria Type II	• Autosomal recessive disorder • Multiple acyl-CoA dehydrogenase • Symptoms include hypotonia, hepatomegaly, acidosis and hypoglycemia	Severe

SECTION II

Part IV: PSYCHIATRIC DISORDERS & THEIR IMPLICATION FOR DISCLOSURE

Psychiatry has come a long way since the days of more or less "theory based psychiatry." What is meant here by "theory based" is that beliefs around etiology and treatment were not supported with much objective or empirical data. Most of it was based on a limited number of case studies. One only needs to look at the theories of Kræplin, Freud, Jung, Piaget, etc, for evidence of this. Today, genetics is invading every field of medicine and psychiatry is no exception.

With the development of molecular biological techniques, scientists have been able to frequently identify the gene on specific loci of chromosomes for many of the neuropsychiatric disorders like Huntington's disease (chromosome 4), Friedreich's Ataxia (chromosome 17) and many others which were outlined in the earlier section of this Handbook. Once there is some evidence of a genetic origin for a disease, usually derived from family, twin and adoption studies the methods of molecular biology can be used to locate their relevant gene(s) and locate the precise abnormality.

In evaluating the claim of a genetic cause, it is important to understand the level of evidence used to support such a claim. The chart below presents levels of evidence by cause and by association.

Highest level of evidence – causality with nearly complete penetrance.	The relationship is 1 to 1. In this case, the presence of a particular gene means the absolute presence of the disease or carrier state. Ex. The presence of the gene at 4p16.3 (Huntington's) is associated with almost complete penetrance (if you have the gene, you will manifest the disease). The pattern of inheritance, as noted in an earlier section of the Handbook, is autosomal dominant inheritance.
Next level of evidence is causality with variable penetrance.	The person possesses the gene but it may or may not be expressed – often jumps a generation. Duchenne's Muscular Dystrophy (X-linked recessive), as seen in the female carrier who may also express or not express the disease, is a good example.
Multifactorial association or polygenic inheritance.	Seen where there is a known association between a gene (PAX1) polymorphism in the gene responsible for methylene – tetrahydrofolate reductase (MTHFR) and the development of a neural tube defect in the newborn. Here, there also has to be an interaction with an environmental circumstance, namely, decreased folate (in the diet), for the disease to be expressed.
Association alone	Here, there is increased prevalence and/or incidence in a population without a clearly demonstrable genetic link. This is the weakest form of evidence.

In addition to the genetic evidence above, psychiatric studies have more frequently depended on population studies in which family, twin and adoption studies are examined to attempt to see if there is an association, what kind and if there is a possible genic association. The chart below summarizes the **pros** and **cons** of these three types of studies.

Type of Study	Pros and Cons
Family Studies	**Pros** • These studies can provide useful information on whether the phenomenon under observation occurs more frequently among blood relatives of an affected individual as compared to the controls. • What other phenomena (if any) are **also** found in association among relatives of an affected individual; that is, what other disorders share a common vulnerability with the phenomenon in question. • Most importantly, does the phenomenon in question share a genetic pattern? Ex. sex-linked, autosomal recessive, etc. **Cons** • The evidence, unless it precisely reproduces a genetic inheritance pattern, tends to follow a polygenic pattern which means sometimes a characteristic is associated but at other times it is not. Thus, the association is at best statistical and correlational. As Thurston, the father of the correlation coefficient said, correlation is an admission of ignorance.

For those interested in reviewing the topic of psychiatric genetics, at a more general level, see, "Review of Psychiatric Genetics" Eds Kendler and Eaves, published by the American Psychiatric Publishing, Inc. ISBN 1-58562-228-1.

Twin Studies	**Pros** Monozygotic or identical twins have the exact same genes as compared to fraternal or dizygotic twins who have about 50% of their genes in common. Thus, by examining **concordance rates** (how often the one twin demonstrates the phenomenon in question, when the other member of the twins demonstrates the same phenomenon in question); one can obtain indirect evidence of a genetic link. Obviously, monozygotic concordance should be closer to 1 to 1 than dizygotic twins if a disorder is genetic. **Cons** Identical twins (monozygotic) are not that common as well, twin studies of dizygotic twins are also moderately rare. The incidence in the normal population [21] is: Monozygotic Twins (identical) 1 in 300 pregnancies Dizygotic Twins (fraternal) 1 in 100 • Often the numbers (N) are very small and it is difficult to have confidence in the results when the N is so small.
Adoption Studies	**Pros** • Represent strong evidence for inheritance disorders. • A group of **affected** subjects, who have been adopted, are studied. Similarly, a group of adopted, **unaffected** individuals are studied as a control and the results are compared. • If the disorder is inherited, one should find an increased risk among the biological relatives of the affected subjects compared to the other three groups. **Cons** • Unless the patterns reproduce a discernible genetic pattern, ex. autosomal recessive, it may be difficult to identify a genetic pattern. This is especially the case in polygenic studies.

[21] Ibid. p. 102

METHODS OF GENETIC ANALYSIS AND THEIR APPLICABILITY TO PSYCHIATRY

Segregation Analysis

There are several methods of formal genetic analysis, while these are important in the study of disease, their utility is often reduced in psychiatric studies. For instance, the powerful tool of **Segregation Analysis**, which is frequently used to determine if a medical disease pattern in families is consistent with a specific genetic mode of transmission is an example. The method is quite powerful. Computer generated analyses is available for not only single major locus inheritance but also available for polygenic and multi-factorial inheritance. When dealing with psychiatric disorders, Nurnberger and Berretini[22] have identified four major confounding variables. These are:

- The existence of variable penetrance – some individuals with a specific predisposition will **not** manifest the disease.
- Phenocopies - some individuals without a genetic predisposition will manifest symptoms of the disease.
- Genetic heterogeneity - more than one type of genetic cause can produce the **same** syndrome.
- Uncertainty regarding the diagnostic boundaries of a syndrome.

These authors conclude:

> **Although segregation analysis is a powerful tool for delineating data from family studies for many disorders, it has been less useful in psychiatry thus far.**

Linkage Analysis

Another powerful tool is genetic linkage analysis. It is based on the idea that normally for any location (locus), an individual caries two alleles or copies of the DNA sequence that defines this locus. Normally, these alleles are transmitted with equal probability 50:50 to each of the offspring – one is from the mother, the other is from the father. However, sometimes these transmissions are not independent but the alleles are inherited together and this is termed "**linked loci.**" These linked loci may undergo recombination during meiosis so that these linked loci are **not always inherited together**.

Now, to try to keep it simple, loci that are not linked tend to be far apart, while loci that are linked tend to be closer together, and this is represented by probability. Thus, two loci that are not closely linked are said to have a probability of 50:50 while the probability that they are linked will be less than 50:50. To put this mathematically, the symbol θ is used to express the probability of linkage (recombination).

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[22] Nurnberger, J. and Berretini, W. Psychiatric Genetics, cited in Current Diagnosis and Treatment in Psychiatry, (eds) Ebert et al; Toronto, Lange Medical Books, 2000, pg. 61.

Thus, non linkage is $\theta = 0.5$, while linkage is $\theta = <0.5$. Thus, an odds ratio (the probability of an event occurring vs it not occurring expressed as a ratio) is used to express this relationship. A logarithmic transformation of the odds ratio is preferred to allow scores from different families to be used. The logarithm of the odds ratio (LOD) is used to define the closeness of the loci.

$$\text{LOD score} = \log_{10} \frac{P(\theta) < 0.5}{P(\theta) = 0.5}$$

Thus, an LOD score of 3 or greater is evidence of linkage and a score of -2 is sufficient to exclude linkage from the sample study. However, psychiatric disorders and disorders of complex inheritance (multifactorial, polygenic, etc.) require higher LOD scores.

Association Studies

In these studies, families are compared; one group of families with a particular disease to a similar group of families (matched for age, sex, ethnicity, etc.) who do not have the disease. Thus, if a particular allele predisposes individuals to the disease under study then it should be present in greater frequency in the disease group versus the control group.

However, in these studies it is difficult to control all the variables and false positives can frequently arise if all the variables are not carefully matched.

The Human Genome

Still in its infancy, these DNA marker studies from human genome project offer some promising possibilities. It is still too early, however, to say what these techniques will show.

Note:

This brief introduction should allow you to read the literature, consultant's notes, etc. with greater ease. This information is provided not to try to make you into geneticists, nor to fetter in any way your judgement – rather, it is provided to allow you to function more cost-effectively; in essence, helping you to identify the precise piece of information you need to make your decision more quickly and accurately. This note should sound a clear warning at drawing conclusions of a genetic link in psychiatric studies without the appropriate controls.

GENETIC STUDIES OF SPECIFIC PSYCHIATRIC DISORDERS

The Affective Disorders

It is important to note that **to date no specific gene has been found for any affective disorder.**

One of the common reasons cited for a request for disclosure is the claim that there is a genetic relationship in affective disorders especially among the direct offspring or first degree relatives, and that this should constitute sufficient reason for disclosure. The comments below look at some of the evidence. It is in no way exhaustive in its coverage; however, it is highly representative of the current literature. By the end of this section, you should be able to better assess such claims made on a psychogenetic basis.

Studies of families have revealed an aggregation of mental illness among relatives of those with affective disorders. The table below shows the lifetime prevalence among relative of these patients from a number of selected studies. Note the degree of variability between the percentages for bipolar and unipolar. **It should be self-evident that there is not a strong case for a clearly genetic pattern. Some of these associations may be attributable to similar exogenous factors such as the environment.**

Lifetime prevalence of affective illness in first-degree relatives of patients and control subjects.[23]

Reference	Morbid Risk (%)	
	Bipolar	Unipolar
Bipolar Probands		
Perris 1966	10.2	0.5
Winokur and Clayton 1967	10.2	20.4
Goetzl et al 1974	2.8	13.7
Helzer and Winokur 1974	4.6	10.6
Mendlewicz and /Rainer	17.7	22.4
James and Chapman 1975	6.4	13.2
Gershon et al 1975	3.8	8.7
Smeraldi et al 1977	5.8	7.1
Johnson and Leeman 1977	15.5	19.8
Pettersen 1977	3.6	7.2
Angst et al 1979, 1980	2.5	7.0
Taylor et al 1980	4.8	4.2
Gershon et al 1981b, 1982	8.0	14.9
Unipolar Probands		
Perris 1966	0.3	6.4
Gershon et al 1975	2.1	14.2
Smeraldi et al 1977	0.6	8.0
Angst et al 1979, 1980	0.1	5.9
Taylor et al 1980	4.1	8.3
Weissman et al 1984	2.1	17.5
Weissman et al 1984	3.4	16.7
Gershon et al 1981b, 1982	2.9	16.6
Normal Probands		
Gershon et al 1975b	0.2	0.7
Weissman et al 1984	1.9	5.6
Gershon et al 1981b, 1992	0.5	5.8

[23] Full references are found in Nurnberger, J. and Berretini, W. Psychiatric Genetics, cited in Current Diagnosis and Treatment in Psychiatry, (eds) Ebert et al; Toronto, Lange Medical Books, 2000, pg. 65.

In a study by the National Institute of Health, 25% of relatives of Bipolar probands were found to have Bipolar disorder or Unipolar disorder (depression) compared to 7% for control subjects. In the same study, when Bipolar and Unipolar prevalence rates were looked at separately, they showed a prevalence rate of 25% vs 20% respectively.[24] The difference between the two groups barely reaches statistical significance. Further, it was shown that 40% of schizoaffective probands have some form of affective illness at some point in their lifetime. While relatives of schizoaffective probands may have schizoaffective illness themselves, relatives of bipolar probands have either bipolar but more likely, unipolar illness.

It has been stated:

> *If pedigrees of patients with affective disorders are considered as a group, it has generally not been possible to fit single-gene models to them.*[25]

Other theories argue for some form of multifactorial or for heterogeneity as the explanations. **It should be clear, however, that at this time, the evidence for a genetic basis of these disorders remain speculative.**

Linkage studies have shown some possible genetic candidates (see the table below). However, attempts to confirm the linkage by other researchers have failed.

Putative linkages for affective disorders*	
Chromosomal location	**Reference**
18P	Berrettini et al., 1993 Stine et al., 1995
21q	Straub et al., 1994 Detera-Wadleigh et al., 1996
Xq26	Pekkarinen et al., 1995
11p15	Egeland et al., 1987 Kelsoe et al., 1991 Gurling et al., 1995
5q	Coon et al., 1993
4p	Blackwood et al., 1996
18q	Freimer et al., 1996 Stine et al., 1995
Other (including 10p, 12q)	Craddock et al., 1994 Ewald et al., 1995 Ginns et al., 1996 NIMH Genetics Initiative 1997

*Full reference is found in Nurnberger and Berrettini 1998.

[24] The data from the National Institute of Health is cited in, Current Diagnosis and Treatment in Psychiatry; Ebert, M; Loosen, P. and Nurcombe, B. (eds). (Toronto, McGraw-Hill, 2000) p. 67.
[25] Ibid.

SOME FACTS BEHIND THE TYPES OF AFFECTIVE DISORDERS

1. **Bipolar Disorder** with Rapid Cycling. This diagnosis is given to those with *four or more episodes of mania or depression per year*. Regrettably, this disorder is relatively resistant to lithium treatment. This disorder appears to arise, "from factors that are separate from genetic vulnerability to bipolar illness and that do not lead to aggregation within families."[26] **Therefore, disclosure is not warranted, in accordance with the legislation.**

2. **Unipolar mania** refers to a patient with Bipolar I disorder who has no history of major depression. They frequently are male, responsive to lithium and on a more detailed follow up, have subclinical depression. This group is only distinguished from other group I disorders on the basis of family history. **Therefore, if a specialist requests disclosure on the basis of bipolar I disorder, for someone potentially belonging to this group, it may be considered, provided that the symptoms have been severe (as understood in the legislation).**

3. **Cyclothymic Disorders:** These are disorders that involve repetitive high and low mood swings that generally do not require major clinical intervention as the severity tends to be mild to moderate. See the DSM-IV.[27] While it may possibly be related to Bipolar Disorder, **it does not meet the test of severity as indicated in the legislation.**

4. **Schizoaffective Disorder**, characterized by psychotic symptoms, intermittently or chronically, between mood episodes. It may share genetic vulnerability factors with schizophrenia and affective illness. A schizoaffective disorder of the bipolar type seems more closely related to mood disorder, whereas schizoaffective disorder of the depressed type may be more closely related to schizophrenia. **The genetic links are not strong enough to merit disclosures as understood in the legislation.**[28] However, they should be looked at carefully case-by-case – see recommendation at the end of this chapter, p.67.

5. **Schizophrenia** – although there is some evidence (inconclusive) that there may be a relationship between schizophrenia and bipolar illness in the relatives of schizophrenia, the evidence is weak. However, bipolar illness has not generally been found in the probands of schizophrenia vs controls. Interestingly, there is no greater prevalence of schizophrenia per se in the probands of Schizophrenia. (See recommendation at the end of this chapter).

6. **Eating Disorders**, anorexia and bulimia, especially the former have a significant association with **morbidity** and **mortality**. They are, therefore, serious disorders. There is evidence of an increased prevalence of affective disorders in the relatives of those with eating disorders and it is similar to the risk in bipolar disorders. **Those with eating disorders, provided they are severe, in accordance with the legislation, should be granted disclosure.**

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[26] Ibid., p. 66.
[27] The Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-T12. (4th ed.), American Psychiatric Association, Washington, D.C., 2000. Pages 398-400.
[28] Losen, Ibid. p. 66.

Family studies of eating disorders[29]		
Study	**Morbid Risk Among First-Degree Relatives**	
Anorexia Nervosa	**Anorexia Probands**	**Control Subjects (*N*)**
Gershon et al 1983	2.0% (99)	0% (265)
Strober et al 1990	4.1% (387)	0% (703)
Bulimia	**Anorexia Probands (*N*)**	**Control Subjects (*N*)**
Gershon et al 1983	4.4% (99)	1.3% (265)
Strober et al 1990	2.6% (387)	1.1% (703)
Bulimia	**Bulimia Probands (*N*)**	**Control Subjects (*N*)**
Kassett et al 1989	2.0% (185)	0% (265)
Strober et al 1990	4.1% (387)	0% (703)

*Full references are found in Nurnberger and Berrettini 1998.

7. **Attention Deficit/Hyperactivity Disorder** (ADHD) is associated with an increased prevalence among relatives of the group, compared to controls of depression. **Since, within the meaning of the legislation, ADHD is not a severe disorder, disclosure should not be granted.** Note: The reverse is *not true* that bipolar and unipolar probands have a higher prevalence of ADHD.

A NOTE ON ALCOHOLISM

Alcoholism is a confounding factor and appears in unexpectedly high frequency in both bipolar and unipolar disorders. There is some evidence, although not particularly strong, that unipolar depressive patients with alcoholism or those with a higher prevalence among their relatives of sociopaths, are a distinct subgroup from other unipolar patients. Some evidence also exists, that alcoholism with comorbid affective disorders may aggregate within families. **It will be discussed under the section on Specific Disease Entities,** p.63.

Nurnberger and Berretini summarize the present state of psychiatric disorders and genetics in this way:

> "**Summary & Empritical Data for Genetic Counseling**
>
> Molecular genetic studies hold great promise for families with affective disorder, particularly bipolar disorder. The availability of DNA markers would make genetic counseling for these disorders much more precise. Such counseling has already begun for families with Huntington's disease. At present, however, the field has not reached the point at which such markers are clinically useful for affective disorder. This is also the case for etiologic markers. Consequently genetic counseling must be based on empirical risk figures."[30]

[29] Ibid. p. 73
[30] Ibid. p. 67

Some Specific Disease Entities That Occur Commonly

The following are all relatively common and a brief review of the genetic evidence is offered here. These include **alcoholism, substance dependency** (other than alcoholism), **Alzheimer's disease, Autism**, and **Tourette's syndrome**.

1. Alcoholism:

Various figures are quoted, but one set that seems to reflect the norm and cited by Nurnberger and Berretini,[31] indicated that 27% prevalence occurred among fathers of alcoholics and 4.9% in mothers. Also, 30.8% of alcoholics have at least one parent who is alcoholic. These rates of prevalence are not seen among controls. There is strong evidence from twin studies for some inheritable disease. At least 40% show some kind of genetic linkage, however, it appears to be multifactorial. It also seems that prevalence increases with severity, in some studies reaching 90%.

Cloninger (1987) suggested that there were two types of alcoholism – Type I and Type II:

- Those with Type I, he termed Milieu-limited. These are males, onset after the age of 25, who manifested problems with loss of control, and have a great deal of guilt and fear about alcohol use.

- Those with Type II have onset before age 25, are unable to abstain from alcohol and are aggressive, often resulting in fights and arrests when drinking. Show less guilt and fear.

Using the above and analyzing data from the Stockholm Adoption Study, it was found that Type I alcoholism, was found increasingly in those adoptees with **both** *genetic* and *environmental* risk factors (i.e., alcoholism in both the biological and adoptive parents). Type I was the most common type as compared to controls who showed only a 4.3% prevalence.

Type II was present in 17% of the adoptees as compared to 1.9% in the controls. The only risk factor was a parent with alcoholism, whereas alcoholism in an adoptive parent made no difference.

Interestingly, adopted daughters from Type II alcoholism showed no increase in alcoholism but an increase in somatization disorders.

Finally, it has also been noticed that various behavioral disorders, conduct disorders, and substance use disorders are more common in the offspring of alcoholic parents – **however, the associations do not follow a clear genetic pattern; therefore, disclosure is not warranted.**

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[31] Ibid., p. 68.

2. Substance Use Disorders (dependency)

Results are less clear for this group and suggest a strong environmental factor. There appears to be an increased prevalence in adoptees whose parent(s) were substance users. At particular risk are the children of opiate-dependent parents for drug dependency, anti-social behaviour, alcoholism and depression. **The associations are multifactorial and should not be grounds for disclosure within the context of the legislation.**

3. Alzheimer's Disease

Interestingly, genetic etiologies for **some** forms of Alzheimer's have been discovered for a small subgroup. Generally, however, the disorder does not show easy inheritability. Early onset of the disease has been associated with a greater likelihood of inheritability, which may be due to **single gene** inheritance. The chart below illustrates some of these single gene studies. Perhaps *the best* known is that of Goates et al, 1991 and reported in *Nature*. The risk to siblings of probands (with at least one parent affected) is 50%. **Therefore, a search should be granted, since within the meaning of the legislation** the condition **is severe and for some types, genetic testing is available.** It is likely that it will not be possible to easily distinguish easily those at high risk, unless you can confirm that at least one parent had the disease before age 70. Even with this cut-off, it is not sufficiently reliable to act as a *sine qua non* as a disease maker. Below are the genes implicated in Alzheimer's disease.

Genes implicated in Alzheimer's Disease[32]

Chromosomal Location	Clinical Correlate	Frequency	Gene Name	Reference
21q	Early onset	Rare	APP	Goate et al 1991
1	Early onset	Rare	Presenilin II	Levy-lahand et al 1995
19	Late onset	Common	ApoE	Strittmatter et al 1993
14	Early onset	Rare	Pesenilin I	Schellenberg et al 1992

4. Autism

Multiple single gene disorders are associated with Autism. The most clearly documented of these is fragile X syndrome (discussed in the genetic section of this Handbook). About 8% of autistic subjects have the cytogenetic fragile X, and 16% of males with Fragile X are autistic. There remain, however, some mysteries. Family studies do not generally provide evidence for a major role of Fragile X mutations in autism. There are associations with other disorders such as neurofibromatosis, tuberous sclerosis and even phenylketonuria. It appears that single-gene abnormalities may serve to initiate the autistic process in some cases. **Fragile X, and Autism should be grounds for granting disclosure, according to the legislative requirements.**

[32] Ibid., p. 70.

5. Tourette's Syndrome

At present, it has been noted that there is a higher incidence among blood relatives of Tourette's Syndrome, of TICS and OCD as well as Tourette's itself.

Prevalence among Probands with 1st degree relatives with Tourette's

Tourette's	8.3%
TICS	16.3%
OCD	9.5%

Presently, there is a collaborative effort to use systematic genomic screening to find gene(s) responsible. To date, however, the evidence is inconclusive. **Tourette's should be decided on a case-by-case basis – you may, therefore, need a consult. Factors favouring granting relate to severity.**

Antisocial Personality Disorders

There have been a number of studies that have demonstrated a higher prevalence among criminals, of antisocial personality disorder, learning disorders, conduct disorders, etc. There is no clear evidence, however, for a genetic basis to this. One study by Brunner[33] et al published in Science in 1993 tried to link 'abnormal behavior(s)' with a point mutation in the structural gene for monoamine oxidase. However, subsequent research has failed to establish this link. Similarly, attempts to link those with XYY males have also failed. In summary then, **conduct disorder and other antisocial personality disorders are not grounds for granting disclosure, as understood within the legislation.**

Anxiety Disorders

Although there is some evidence that panic disorders might possibly be passed from person to person, there is little evidence to support this idea for Generalized Anxiety Disorders (GAD). What may be said of GAD, Phobic reactions and Panic disorders is that there is some degree of increased risk for probands. However, the genetics has not been worked out well enough for it to be used to guide your decisions. **The presence of these conditions is not sufficient to merit disclosure, as understood within the legislation.**

Obsessive-Compulsive Disorders (OCD)

When OCD appears in the familial context of Tourette's syndrome (c.f. p. 64), the OCD should be considered as part of Tourette's unless there is overwhelming evidence to the contrary. However, the majority of OCD patients have no first degree relatives affected by Tourette's syndrome. **OCD should not constitute grounds for disclosure, within the meaning of the legislation.**

Nurnberger states:[34]

> **There is limited evidence from family, twin, and adoption studies regarding the inheritance of OCD. Although OCD may be familial, there is insufficient data from twin studies and no data from adoption studies.**

The information provided should allow you to better understand:

(1) The medical basis for accepting or rejecting an argument based on diagnosis and family history.
(2) The medical information provided for a specific case.
(3) What information may still be needed in order for you to make a decision?
(4) Whether you should seek an outside consult.

The Handbook should not replace common sense, your experience or in anyway fetter your judgement.

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[33] Brunner HG, et al Abnormal behavior associated with a point mutation in the structural gene for monoamino oxidase A. *Science* 1993.262:578.
[34] Nurnberger, cited in Current Diagnosis and Treatment. Ibid., p. 75.

Recommendation

In spite of the fact that there is no clear genetic 1 to 1 concordance between psychiatric illness and any particular gene model, there is evidence that some sort of genetic factor(s) are at play. Where there is a significant risk for a psychiatric disease that is severe and incapacitating and that at least one parent has had the disease, **disclosure should be strongly considered**. **Significant risk should be considered to be a 9-10 fold increased risk of an affected offspring.** Factors favouring disclosure for these high risk group as well as many other psychiatric group are:

(1) A letter from a geneticist stating that for a specific disease there is a need to disclose as others are at risk. Note however, **the condition must be severe, as defined in the legislation, and meet all the other conditions under the legislation**.

(2) A letter from a treating psychiatrist stating that the family history is essential to the diagnosis and the absence of said information would seriously affect the treatment, or lead to increased risk for the patient. Again, **the condition must not be trivial but severe as understood within the legislation, and should meet all the other conditions under the legislation. The potential benefit should clearly be stated by the psychiatrist as well as the harm of withholding this information and why they apply to this specific case.**

The chart below is from Nurnberger and Berretini[35] and provides a good indication of the increased risk for offspring of those with at least one parent affected by a mental illness. Note, those with a risk equal to or greater than a 9-10 fold risk.

Family study data for genetic counselling		
Family History*	**Unselected General Population Risk**	**Increased Risk for Offspring**
Unipolar disorder (UP)	6%	2-fold (16%) for UP 4-fold (4%) for BP
Bipolar disorder (BP)	1%	9-fold (9%) for BP 2-fold (16%) for UP
Schizophrenia (SZ)	1%	10-fold (10%) for SZ 2-fold (15%) for UP
Alcoholism	5% males, 1% females	5-fold (27% for males, 5% for females)
Panic disorder	0.5%	12-fold (6%)
Tourette's syndrome	0.25%	100-fold (25%)
Alzheimer's disease	3%	5-fold (15%) at age 75
Attention-deficit/hyperactivity disorder	3%	5-fold (15%)
Anorexia nervosa	0.5%	10-fold (5%)

* These data assume that only one parent is affected.

Consideration for disclosure should be given to those with a 9-10 fold increase, or greater, of having an affected offspring.

[35] Ibid., p. 79.

PART V

MEDICAL DISORDERS

There is a group of disorders for which there is an increased occurrence of the disorder among 'blood' relatives, without a clear and precise genetic pattern. These disorders tend to fall into one of two groups:

1) Those disorders, quite frequently manifesting in later life, with polysymptoms and whose consequences can be life threatening (ex. Systemic Lupus Erythematosus or SLE).

2) A disorder appearing 'de novo' or 'out of the blue', with no previous family history (ex. Congenital Heart Disease).

In each of these two groups, a search should be considered if the potential consequences could be life threatening, Ex. Renal Disease from SLE or if monitoring of offspring is required, ex. Hereditary hemochromatosis.

These cases will have to be judged more on a case by case basis than by diagnostic label or category. The factors of importance in family are:

(i) Severity
(ii) Treatability
(iii)Implication for reproduction
(iv)Risk profile of <u>not</u> informing a client
(v) Knowledge of an affected relative crucial to the diagnosis
(vi)Increased surveillance or monitoring will be required of asymptomatic offspring.

Below are some of the most common disorders falling into these categories. In all cases the diagnosis must be firmly established.

Rheumatological Diagnosis		
Inheritance Pattern	**Description**	**Examples**
Systemic Lupus Erythematosus	• Incidence is 1 in 2,000. Female to male ratio is 2:1. Peak onset between 15-40 years of age. • Mortality higher in minorities and those with low socio-economic status. • Associated with HLA DR_2 and DR_3. • Pregnancy may precipitate the appearance of the disease but does not alter incidence or prevalence. • Must eliminate "drug" induced lupus from this group.	Grant

	• Serious manifestation is to organ systems such as kidney, heart, lung, etc.	
Rheumatoid Arthritis	• Diagnosis must be that of a true Rheumatoid Arthritis. • Affects all ethnic groups but highest among First Nations people. • Also found in increased incidence among Israelis and Asian Indians. ***Grant* for those with organ system disease.** Ex. renal, heart, blood, nervous system, lung, etc.	Grant (see note on grant)
Systemic Sclerosis (Scleroderma)	• Has a variable prognosis. The local form (Morphea) is not life threatening but the more severe form, which is systemic can be life threatening. • Female to male ratio: 2-3:1 • A limited form of the disease known as CREST can occur and is rarely life threatening. • Severe form with organ system involvement can be life threatening, especially: ○ Cardiac ○ Pulmonary ○ Renal ○ Gastro-intestinal	Grant if systemic
Idiopathic Inflammatory Myopathies	• There are two types: (i) Polymyositis (ii) Dermatomyositis Both may have severe side effects: 1) Dysphagia, interstitial lung disease (polymyositis) 2) Pericarditis, heart and more rarely lung disease (dermatomyositis).	Grant if systemic
Vasculitis	Two types: 1) Polyarteritis Nodosa (PAN) 2) Microscopic Polyangitis (MPA) If these are severe enough to manifest in systemic disease such as: • Renal • Lung • Heart • Blood vessels • Neurological Then, they should be granted.	Pass if there are systemic symptoms
Giant Cell Arthritis	• Grant if there are systemic manifestations that are severe.	Grant if systemic

Wegner's Granulomatosis	Grant if there are systemic signs of lung, renal or cardiac abnormalities. Occasionally, there will be neurologic symptoms that are severe, in which case you should grant.	Grant if there are systemic signs.

Cardiovascular Disease

	Congenital Heart disease • Mitral stenosis/regurgitation • Aortic stenosis/regurgitation • Pulmonary or tricuspid valvular disease • Marfan's with AI, ASD, MI • Patent ductus arteriosis • Eisenmenger's syndrome (Reversal of the left to right shunt due to pulmonary hypertension).	Grant

Pulmonary Disease

	• Pulmonary disease secondary to cystic fibrosis. • Hypersensitivity pneumonitis (recurrent) • Lung disease due to Rheumatoid Arthritis, Systemic Lupus, Sarcoidosis • Histocytosis X	Grant

Neurological Disease

	• Spinal bifida or occulta • Multiple Sclerosis • Parkinson's Disease • Amyotrophic Lateral Sclerosis (ALS) • Tourette's syndrome • Von Recklinghausen's disease (neurofibromatosis)	Grant

Haematology

	Lymphomas • Haemorrhagic and platelet • Hodgkin's and non-Hodgkin's Lymphomas • Leukaemia • Hemophilia • Hereditary hemochromatosis	Grant

Endocrine		
	• Thyroid Cancer • Parophthalmia • Cushing's Disease • Pheochromocytoma	Grant

Gastro-Intestinal Disease

	• Inflammatory Bowel Disease (1) Ulcerative Colitis (2) Crohn's Disease (3) Familial adenomatous polyposis	1 & 2 Grant #3

Renal Disease

	Congenital Renal Abnormalities • Duplication (Kidney or collecting systems) • Absence of a kidney • Polycystic kidney • Structural abnormalities of the bladder and urethra	Do not grant

Vision Disease

	• Retinitis pigmentosa • Macular Degenerations	Grant

Ear, Nose, Throat Disease

	Any structural abnormalities Ex. • Deafness from birth • Cleft lip or palate	Do not grant

Malignant Disease

	While not all cancers are genetic, higher vigilance cases save lives. All cases for cancer should be considered if (1) screening is available (2) knowledge of the disease would result in earlier screening than current guidelines would recommend or where there is a reliable and specific genetic test(s). Ex. Familial Ovarian Cancer	This can be difficult to decide – you may need a consult.

Appendices

Glossary of Genetic Terms

Achondroplasia -- the most common and well known form of short limbed dwarfism characterized by a normal trunk size with disproportionally short arms and legs, and a disproportionally large head; autosomal dominant condition.

Advanced maternal age -- women over age 34 (age 35 at delivery) at increased risk for nondisjunction trisomy in fetus.

Alcoholism -- a chronic and progressive condition characterized by the inability to control the consumption of alcohol.

Allele -- an alternative form of a gene; any one of several mutational forms of a gene.

Alpha-fetoprotein (AFP) -- a protein excreted by the fetus into the amniotic fluid and from there into the mother's bloodstream through the placenta.

Alu repetitive sequence -- the most common dispersed repeated DNA sequence in the human genome accounting for 5% of human DNA. The name is derived from the fact that these sequences are cleaved by the restriction endonuclease Alu.

Amino acid sequence -- the linear order of the amino acids in a protein or peptide.

Amniocentesis -- prenatal diagnosis method using cells in the amniotic fluid to determine the number and kind of chromosomes of the fetus and, when indicated, perform biochemical studies.

Amniocyte -- cells obtained by amniocentesis.

Amplification -- any process by which specific DNA sequences are replicated disproportionately greater than their representation in the parent molecules.

Aneuploidy -- state of having variant chromosome number (too many or too few). (i.e. Down syndrome, Turner syndrome).

Angelman syndrome -- a condition characterized by severe mental deficiency, developmental delay and growth deficiency, puppet-like gait and frequent laughter unconnected to emotions of happiness.

Apert syndrome -- a condition caused by the premature closure of the sutures of the skull bones, resulting in an altered head shape, with webbed fingers and toes. Autosomal dominant.

Artificial insemination -- the placement of sperm into a female reproductive tract or the mixing of male and female gametes by other than natural means.

Autosome -- a nuclear chromosome other than the X- and Y-chromosomes.

Autoradiograph -- a photographic picture showing the position of radioactive substances in tissues.

Bacteriophage -- a virus whose host is a bacterium; commonly called phage.

Barr body -- the condensed single X-chromosome seen in the nuclei of somatic cells of female mammals. base pair a pair of hydrogen-bonded nitrogenous bases (one purine and one pyrimidine) that join the component strands of the DNA double helix.

Base sequence -- a partnership of organic bases found in DNA and RNA; adenine forms a base pair with thymine (or uracil) and guanine with cytosine in a double-stranded nucleic acid molecule.

Baysian analysis -- a mathematical method to further refine recurrence risk taking into account other known factors.

Becker muscular dystrophy -- X-linked condition characterized by progressive muscle weakness and wasting; manifests later in life with progression less severe than Duchenne muscular dystrophy.

Carrier -- an individual heterozygous for a single recessive gene.

cDNA -- complementary DNA produced from a RNA template by the action of RNA- dependent DNA polymerase.

Centromere -- a region of a chromosome to which spindle traction fibers attach during mitosis and meiosis; the position of the centromere determines whether the chromosome is considered an acrocentric, metacentric or telomeric chromosome.

Charcot-Marie Tooth disease -- a condition characterized by degeneration of the motor and sensory nerves that control movement and feeling in the arm below the elbow and the leg below the knee; transmitted in autosomal dominant, autosomal recessive and X-linked forms.

Chorionic villus sampling -- an invasive prenatal diagnostic procedure involving removal of villi from the human chorion to obtain chromosomes and cell products for diagnosis of disorders in the human embryo.

Chromosome -- in the eukaryotic nucleus, one of the threadlike structures consisting of chromatin and carry genetic information arranged in a linear sequence.

Chromosome banding -- a technique for staining chromosomes so that bands appear in a unique pattern particular to the chromosome.

Cleft lip/palate -- congenital condition with cleft lip alone, or with cleft palate; cause is thought to be multifactorial.

Clone -- genetically engineered replicas of DNA sequences.

Cloned DNA -- any DNA fragment that passively replicates in the host organism after it has been joined to a cloning vector.

Codon -- a sequence of three nucleotides in mRNA that specifies an amino acid.

Consanguinity -- genetic relationship. Consanguineous individuals have at least one common ancestor in the preceding few generations.

Conservative change -- an amino acid change that does not affect significantly the function of the protein.

Contiguous genes -- genes physically close on a chromosome that when acting together express a phenotype.

Cosmids -- plasmid vectors designed for cloning large fragments of eukaryotic DNA; the vector is a plasmid into which phage lambda cohesive end sites have been inserted.

CpG islands -- areas of multiple CG repeats in DNA.

Cri-du-chat syndrome -- a chromosomal condition (monosomy 5p). Name comes from the distinctive mewing cry of affected infants; characterized by significant mental deficiency, low birthweight, failure to thrive and short stature; deletion of a small section of the short arm of chromosome 5.

Crossovers -- the exchange of genetic material between two paired chromosome during meiosis.

Cornelia de Lange syndrome -- condition involving growth deficiency, significant developmental delay, anomalies of the extremities and a characteristic facial appearance.

Cytogenetics -- the study of chromosomes.

Cystic fibrosis -- an autosomal recessive genetic condition of the exocrine glands, which causes the body to produce excessively thick, sticky mucus that clogs the lungs and pancreas, interfering with breathing and digestion.

Degenerate codon -- a codon that specifies the same amino acid as another codon.

Deletion -- the loss of a segment of the genetic material from a chromosome.

Deletion mapping -- the use of overlapping deletions to localize the position of an unknown gene on a chromosome or linkage map.

Disease -- any deviation from the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms and signs whose pathology and prognosis may be known or unknown.

DMD -- Duchenne muscular dystrophy.

DNA fingerprint technique -- a method employed to determine differences in amino acid sequences between related proteins; relies upon the presence of a simple tandem-repetitive sequences that are scattered throughout the human genome.

DNA hybridization -- a technique for selectively binding specific segments of single-stranded (ss) DNA or RNA by base pairing to complementary sequences on ssDNA molecules that are trapped on a nitrocellulose filter.

DNA probe -- any biochemical used to identify or isolate a gene, a gene product, or a protein.

DNA sequencing -- "plus and minus" or "primed synthesis" method, developed by Sanger, DNA is synthesized in vitro in such a way that it is radioactively labeled and the reaction terminates specifically at the position corresponding to a given base; the "chemical" method, ssDNA is subjected to several chemical cleavage protocols that selectively make breaks on one side of a particular base.

DOE -- Department of Energy.

Dominant -- alleles that determine the phenotype displayed in a heterozygote with another (recessive) allele.

Down syndrome -- a type of mental deficiency due to trisomy (three copies) of autosome 21, a translocation of 21 or mosaicism.

Duchenne/Becker muscular dystrophy -- the most common and severe form of muscular dystrophy; transmitted as an X-linked trait. X-linked recessive. Symptoms include onset at 2-5 years with difficulty with gait and stairs, enlarged calf muscles, progression to wheelchair by adolescence, shortened life span.

Dystonia -- neurologic condition involving repeated twisting and movement. Involves a variety of muscle groups. Intelligence not effected. Three forms: childhood - autosomal dominant, autosomal recessive, adult-acquired.

Dwarfism -- conditions of short stature with adult height under 4'10" as adult, usually with normal intelligence and lifespan. Ehlers Danlos Syndrome connective tissue condition including problems with tendons, ligaments, skin, bones, cartilage, and membranes surrounding blood vessels and nerves. Symptoms include joint laxity, elastic skin, dislocations. Many forms: autosomal dominant, autosomal recessive, X-linked forms.

ELSI -- ethical, legal and social implications (of HGP).

Endonuclease -- an enzyme that breaks the internal phosphodiester bonds in a DNA molecule.

Ethics -- the study of fundamental principles which defines values and determines moral duty and obligation.

Erythrocytes -- the hemoglobin-containing cell found in the blood of vertebrates.

Euchromatin -- the chromatin that shows the staining behavior characteristic of the majority of the chromosomal complement.

Eugenics -- the improvement of humanity by atering its genetic composition by encouraging breeding of those presumed to have desirable genes.

Exons -- portion of a gene included in the trancript of a gene and survives processing of the RNA in the cell nucleus to become part of a spliced messenger of a structural RNA in the cell cytoplasm; an exon specifies the amino acid sequence of a portion of the complete polypepde.

Fetal alcohol syndrome -- a link between excessive alcohol consumption during pregnancy and birth defects; characteristics inlude small head and eyes, folds of the skin that obscure the inner juncture of the yelids, short, upturned nose, and thin lips.

FISH -- florescent in situ hybridization: a technique for uniquely identifying whole chromosomes or parts of chromosomes using florescent tagged DNA.

5' - end -- the end of a polynucleotide with a free (or phosphorylated or capped) 5' - hydroxyl group; transcription/translation begins at this end.

Fragile sites -- a non-staining gap of variable width that usually involves both chromatids and is always at exactly the same point on a specific chromosome derived from an individual or kindred.

Fragile-X syndrome -- X-linked trait; the second most common identifiable cause of genetic mental deficiency.

Gamete -- an haploid cell.gel electrophoresis the process by which nucleic acids (DNA or RNA) or proteins are separated by size according to movement of the charged molecules in an electrical field.

Gene -- a hereditary unit that occupies a certain position on a chromosome; a unit that has one or more specific effects on the phenotype, and can mutate to various allelic forms.

Gene amplification -- any process by which specific DNA sequences are replicated disproportionately greater than their representation in the parent molecules; during development, some genes become amplified in specific tissues.

Gene map -- the linear arrangement of mutable sites on a chromosome as deduced from genetic recombination experiments.

Gene therapy -- addition of a functional gene or group of genes to a cell by gene insertion to correct an hereditary disease.

Genetic counseling -- the educational process that helps individuals, couples, or families to understand genetic information and issues that may have an impact on them.

Genetic linkage map -- a chromosome map showing the relative positions of the known genes on the chromosomes of a given species.

Genetic screening -- testing groups of individuals to identify defective genes capable of causing hereditary conditions.

Genetic variation -- a phenotypic variance of a trait in a population attributed to genetic heterogeneity.

Genome -- all of the genes carried by a single gamete; the DNA content of an individual, which includes all 44 autosomes, 2 sex chromosomes, and the mitochondrial DNA.

Genotype -- genetic constitution of an organism.

Germ cell -- a sex cell or gamete (egg or spermatozoan).Haldane equation Haldane's law: the generalization that if first generation hybrids are produced between two species, but one sex is absent, rare, or sterile, that sex is the heterogamic sex.

Hardy-Weinberg Law -- the concept that both gene frequencies and genotype frequencies will remain constant from generation to generation in an infinitely large, interbreeding population in which mating is at random and there is no selection, migration or mutation.

Heterozygote -- having two alleles that are different for a given gene.

Hemophilia -- a sex-linked disease in humans in which the blood-clotting process is defective.

Heterogeneity -- the production of identical or similar phenotypes by different genetic mechanisms.

HGP -- Human Genome Project.

HHMI -- Howard Hughes Medical Institute.

Homologous chromosomes -- chromosomes that pair during meiosis; each homologue is a duplicate of one chromosome from each parent.

Homozygote -- having identical alleles at one or more loci in homologous chromosome segments.

Housekeeping genes -- those genes expressed in all cells because they provide functions needed for sustenance of all cell types.

HUGO -- Human Genome Organization.

Huntington disease -- a disease characterized by irregular, spasmodic involuntary movements of the limbs and facial muscles, mental deterioration and death, usually within 20 years of the onset of symptoms.

Hybridization -- the pairing of a single-stranded, labeled probe (usually DNA) to its complementary sequence.

Ichthyosis -- any of several hereditary or congenital skin conditions; skin of affected individuals has a dry, scaly appearance.

Imprinting -- a chemical modification of a gene allele which can be used to identify maternal or paternal origin of chromosome.

Incomplete penetrance -- the gene for a condition is present, but not obviously expressed in all individuals in a family with the gene.

In situ hybridization -- hybridization of a labeled probe to its complementary sequence within intact, banded chromosomes.

Introns -- a segment of DNA (between exons) that is transcribed into nuclear RNA, but are removed in the subsequent processing into mRNA.

Isochromosome -- a metacentric chromosome produced during mitosis or meiosis when the centromere splits transversely instead of longitudinally; the arms of such chromosome are equal in length and genetically identical, however, the loci are positioned in reverse sequence in the two arms.

Klinefelter syndrome -- an endocrine condition caused by a an extra X-chromosome (47,XXY); characterized by the lack of normal sexual development and testosterone, leading to infertility and adjustment problems if not detected and treated early.

Karyotype -- a set of photographed, banded chromosomes arranged in order from largest to smallest.

Ligase -- an enzyme that functions in DNA repair.

Linkage -- the greater association in inheritance of two or more nonallelic genes than is to be expected from independent assortment; genes are linked because they reside on the same chromosome.

Linkage -- analysis of pedigree the tracking of a gene through a family by following the inheritance of a (closely associated) gene or trait and a DNA marker.

Lod score -- logarithm of the odd score; a measure of the likelihood of two loci being within a measurable distance of each otner.

Marfan syndrome -- autosomal dominant condition of connective tissue; affects the skeletal, ocular and cardiovascular systems.

Marker -- a gene with a known location on a chromosome and a clear-cut phenotype, used as a point of reference when mapping a new mutant.

Meiosis -- the doubling of gametic chromosome number.

Methylation -- addition of a methyl group (-CH3) to DNA or RNA.

Methylmalonic acidemia -- a group of conditions characterized by the inability to metabolize methylmalonic acid or by a defect in the metabolism of Vitamin B12.

Missense mutation -- a change in the base sequence of a gene that alters or eliminates a protein.

Mitochondrial DNA -- the mitochondrial genome consists of a circular DNA duplex, with 5 to 10 copies per organelle.

Mitosis -- nuclear division.

mRNA -- messenger RNA; an RNA molecular that functions during translation to specify the sequence of amino acids in a nascent polypeptide.

Multifactorial -- a characteristic influenced in its expression by many factors, both genetic and environmental.

Mutation -- process by which genes undergo a structural change.

Myotonic dystrophy -- a combination of progressive weakening of the muscles and muscle spasms or rigidity, with difficulty relaxing a contracted muscle; inherited as an autosomal dominant trait.

Neurofibromatosis -- one of the most common single gene conditions affecting the human nervous system; in most cases, "cafe au lait" spots, are the only symptom; inherited as an autosomal dominant trait, with 50% being new mutations.

NIH -- National Institutes of Health.

Nonsense mutation -- a mutation in which a codon is changed to a stop codon, resulting in a truncated protein product.

Noonan syndrome -- a condition characterized by short stature and ovarian or testicular dysfunction, mental deficiency, and lesions of the heart.

Northern analysis -- a technique for transferring electrophoretically resolved RNA segments from an agarose gel to a nitrocellulose filter paper sheet via capillary action.

Nucleotide -- one of the monomeric units from which DNA or RNA polymers are constructed; consists of a purine or pyrimidine base, a pentose sugar and a phosphoric acid group.

Oncogenes -- genes involved in cell cycle control (growth factors, growth factor regulator genes, etc), a mutation can lead to tumor growth.

Osteogenesis imperfecta -- a condition also known as brittle bone disease; characterized by a triangular shaped face with yellowish brown teeth, short stature and stunted growth, scoliosis, high pitched voice, excessive sweating and loose joints.

Parthenogenesis -- the development of an individual from an egg without fertilization.

PCR -- polymerase chain reaction; a technique for copying the complementary strands of a target DNA molecule simultaneously for a series of cycles until the desired amount is obtained.

Pedigree -- a diagram of the heredity of a particular trait through many generations of a family.

Phenotype -- observable characteristics of an organism produced by the organism's genotype interacting with the environment.

Physical map -- map where the distance between markers is the actual distance, such as the number of base pairs.

PKU -- phenylketonuria, an enzyme deficiency condition characterized by the inability to convert one amino acid, phenylalanine, to another, tyrosine, resulting in mental deficiency. plasmid double-stranded, circular, bacterial DNA into which a fragment of DNA from another organism can be inserted.

Pleiotropy -- the phenomenon of variable phenotypes for a number of distinct and seemingly unrelated phenotypic effects.

Polycystic kidney disease (PKD) -- a group of conditions characterized by fluid filled sacs that slowly develop in both kidneys, eventually resulting in kidney malfunction.

Polymerase -- any enzyme that catalyzes the formation of DNA or RNA from deoxyribonucleotides or ribonucleotides.

Prader-Willi syndrome -- a condition characterized by obesity and insatiable appetite, mental deficiency, small genitals, and short stature. May be deletion of #15 chromosome.

Predisposition -- to have a tendency or inclination towards something in advance.

Presymptomatic diagnosis -- diagnosis of a genetic condition before the appearance of symptoms.

Primer -- nucleotides used in the polymerase chain reaction to initiate DNA synthesis at a particular location.

Probability -- the long term frequency of an event relative to all alternative events, and usually expressed as decimal fraction.

Proband -- individual in a family who brought the family to medical attention.

Probe -- single-stranded DNA labeled with radioactive isotopes or tagged in other ways for ease in identification.

Prognosis -- prediction of the course and probable outcome of a disease.

Proteus syndrome -- a condition characterized by distorted asymmetric growth of the body and enlarged head, enlarged feet, multiple nevi on the skin; mode of inheritance is unknown.

Public policy -- a set of action guidelines or rules that result from the actions or lack of actions of governmental entities.

Recessive -- a gene that is phenotypically manifest in the homozygous state but is masked in the presence of a dominant allele.

Recombination -- the natural process of breaking and rejoining DNA strands to produce new combinations of genes and, thus, generate genetic variation. Gene crossover during meiosis.

Repeat sequences -- the length of a nucleotide sequence that is repeated in a tandem cluster.

Retinitis pigmentosa -- group of hereditary ocular disorders with progressive retinal degeneration. Autosomal dominant, autosomal recessive, and x-linked forms.

Retinoblastoma -- a childhood malignant cancer of the retina of the eye. reverse transcriptase viral enzyme used to make cDNA.

RFLP -- restriction fragment length polymorphism; variations occurring within a species in the length of DNA fragments generated by a species endonuclease.

Ribosomal protein -- one of the ribonucleoprotein particles that are the sites of translation.

Rubinstein-Taybi syndrome -- condition with multiple congenital anomalies including: mental deficiency, broad thumbs, small head, broad nasal bridge and beaked nose.

Sanger sequence -- "plus and minus" or "primed synthesis" method; DNA is synthesized so it is radioactively labeled and the reaction terminates specifically at the position corresponding to a given base.

Selection -- the process of determining the relative share allotted individuals of different genotypes in the propagation of a population; the selective effect of a gene can be defined by the probability that carriers of the gene will reproduce.

Sex determination -- the mechanism in a given species by which sex is determined; in many species sex is determined at fertilization by the nature of the sperm that fertilizes the egg.

Sickle cell anemia -- an hereditary, chronic form of hemolytic anemia characterized by breakdown of the red blood cells; red blood cells undergo a reversible alteration in shape when the oxygen tension of the plasma falls slightly and a sickle-like shape forms.

Somatic cell hybrid -- hybrid cell line derived from two different species; contains a complete chromosomal complement of one species and a partial chromosomal complement of the other; human/hamster hybrids grow and divide, losing human chromosomes with each generation until they finally stabilize, the hybrid cell line established is then utilized to detect the presence of genes on the remaining human chromosome.

Somatic mutation -- a mutation occurring in any cell that is not destined to become a germ cell; if the mutant cell continues to divide, the individual will come to contain a patch of tissue of genotype different from the cells of the rest of the body.

Southern blotting -- a technique for transferring electrophoretically resolved DNA segments from an agarose gel to a nitrocelluose filter paper sheet via capillary action; the DNA segment of interest is probed with a radioactive, complementary nucleic acid, and its position is determined by autoradiography.

Spina bifida -- a congenital condition that results from altered fetal development of the spinal cord, part of the neural plate fails to join together and bone and muscle are unable to grow over this open section.

Syndrome -- a recognizable pattern or group of multiple signs, symptoms or malformations that characterize a particular condition; syndromes are thought to arise from a common origin and result from more than one developmental error during fetal growth.

Tay-Sachs disease -- a fatal degenerative disease of the nervous system due to a deficiency of hexosamidase A, causing mental deficiency, paralysis, mental deterioration, and blindness; found primarily but not exclusively among Ashkenazi Jews. Autosomal recessive.

Teratogens -- any agent that raises the incidence of congenital malformations.

3' - end -- the end of a polynucleotide with a free (or phosphorylated) 3' - hydroxyl group.

Trait -- any detectable phenotypic property of an organism.

Transduction -- the transfer of bacterial genetic material from one bacterium to another using a phage as a vector.

Transferase -- enzymes that catalyze the transfer of functional groups between donor and acceptor molecules.

Transcription -- the formation of an RNA molecule upon a DNA template by complementary base pairing.

Translation -- the formation of a polypeptide chain in the specific amino acid sequence directed by the genetic information carried by mRNA.

Translocation -- a chromosome aberration which results in a change in position of a chromosomal segment within the genome, but does not change the total number of genes present.

Triplet code -- a code in which a given amino acid is specified by a set of three nucleotides.

Tumor suppressor gene -- genes that normally function to restrain the growth of tumors; the best understood case is for hereditary retinoblastoma.

Transgenic organism -- one into which a cloned genetic material has been experimentally transferred, a subset of these foreign gene express themselves in their offspring.Turner syndrome a chromosomal condition in females (usually 45,XO) due to monosomy of the X- chromosome; characterized by short stature, failure to develop secondary sex characteristics, and infertility.

UNESCO -- United National Educational, Scientific, and Cultural Organization.

VNTR -- variable number tandem repeats; any gene whose alleles contain different numbers of tandemly repeated oligonucleotide sequences.

Vector -- a self-replicating DNA molecule that transfers a DNA segment between host cells.

Von Hippel-Lindau syndrome -- an autosomal dominant condition characterized by the anomalous growth and proliferation of blood vessels on the retina of the eye and the cerebellum of the brain; cysts and cancers in the kidneys, pancreas, and adrenal glands.

Western blotting analysis -- a technique used to identify a specific protein; the probe is a radioactively labeled antibody raised against the protein in question.

X-inactivation -- the repression of one of the two X-chromosomes in the somatic cells of females as a method of dosage compensation; at an early embryonic stage in the normal female, one of the two X-chromosomes undergoes inactivation, apparently at random, from this point on all descendent cells will have the same X-chromosome inactivated as the cell from which they arose, thus a female is a mosaic composed of two types of cells, one which expresses only the paternal X-chromosome, and another which expresses only the maternal X-chromosome.

XYY syndrome -- genetic condition in males with extra Y chromosome (in 1 in 1000 male births). Symptoms: tall stature (over 6'), may including sterility, developmental delay, learning problems.

YAC -- yeast artificial chromosome; a linear vector into which a large fragment of DNA can be inserted; the development of YAC's in 1987 has increased the number of nucleotides which can be cloned.

Zoo blot -- northern analysis of mRNA from different organisms.[36]

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[36] Compiled by the Genetics Education Center, University of Kansas Medical Center

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